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ORIGINAL ARTICLES.

RHEUMATIC HEART DISEASE COMPLICATING PREGNANCY.

A STUDY OF 61 FATALITIES.

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IN Philadelphia during the decade 1931 to 1940 there has been no significant decrease in the maternal death rate due to rheumatic heart disease. The rate has remained between 2 and 3 per 10,000 live births for the greater part of the 10-year period. This record offers a striking contrast to the reduction in the total maternal death rate during the same 10 years. The latter rate has shown a steady decline from 7.9 deaths per 1000 live births in 1931 to 3.1 in 1940.

We have been interested, therefore, in determining whether the incidence of maternal deaths due to rheumatic heart disease has been reduced to a minimum, and, if not, whether means might be found for preventing fatalities resulting from this disease.

Method. Through the courtesy of the Maternal Welfare Committee of the local County Medical Society, the abstracted case records of all maternal deaths occurring in Philadelphia during the decade 1931 to 1940 were examined. The records of patients having heart disease or suspected of having it were segregated. After further reference to the hospitals' or physicians' records of this group, a selected list of cases was obtained which met certain requirements. First, the presence of rheumatic heart disease had been established by adequate clinical or postmortem evidence; and second, death had resulted primarily from the heart disease or from an

obstetrical procedure employed because of it. The study was limited to the rheumatic form of the disease because this is the principal form of heart disease encountered in women of childbearing age; it is responsible for the great majority of maternal deaths due to heart disease.

In the decade under consideration, there were 307,015 live births and 1789 maternal deaths in Philadelphia. Of these there were 61 cases which met the above requirements and are the basis for this analysis.

Preventability of Deaths. Of the 61 deaths in this series, 20 were regarded as preventable by the Maternal Welfare Committee.* In addition, a number of cases which were judged as non-preventable did not receive ideal care as outlined by such authorities as Stander and Kuder[10] and Hamilton,[4b] and from this point of view, may also have been preventable. Therefore, it is evident that the maternal death rate in Philadelphia due to rheumatic heart disease can be further reduced.

What then can be done to reduce this rate? Our study attempts to show the manner in which the deaths occurred and, in addition, certain of the important factors contributing to the fatalities. By so doing, it is our purpose to reëmphasize some of the special problems which must be successfully combated in the treatment of pregnant cardiac patients in order to lower the death rate among this group.

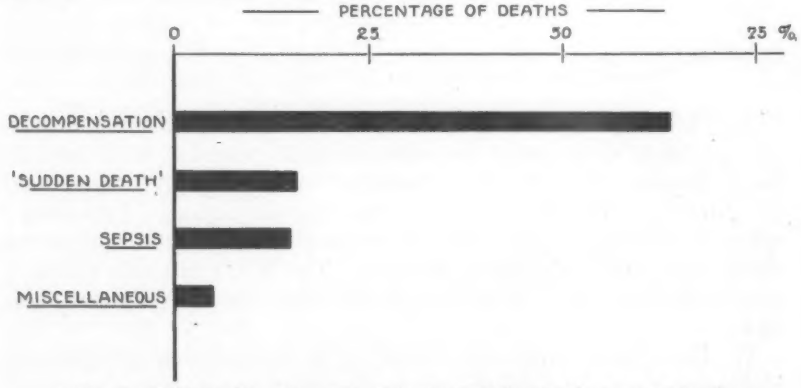

FIG. 1.—Distribution of maternal death according to the type of death.

Manner of Death (Fig. 1). Cardiac decompensation, including pulmonary edema, accounted for 39 (64%) fatalities. Sudden exitus, as from embolism, accounted for 10 (16%) deaths; this group probably also included several instances of acute congestive failure. Puerperal sepsis with terminal cardiac failure was responsible for 9 (15%) deaths. Of the remaining 3 (5%) fatalities, 1 was due to

* Since 1931, each maternal death which has occurred in Philadelphia has been analyzed and discussed by this committee. Decisions are thereby reached as to the preventability of the death and the factors responsible for it.

subacute bacterial endocarditis, 1 to acute antepartal endocarditis and 1 to an uncertain cause.

Relationship of Death to Pregnancy and Delivery (Figs. 2 and 3). Fifty-two (85%) of the patients died after the 28th week of gestation and 41 (67%) after the 35th week. Although it is apparent that death was generally delayed until the late stages of gestation,

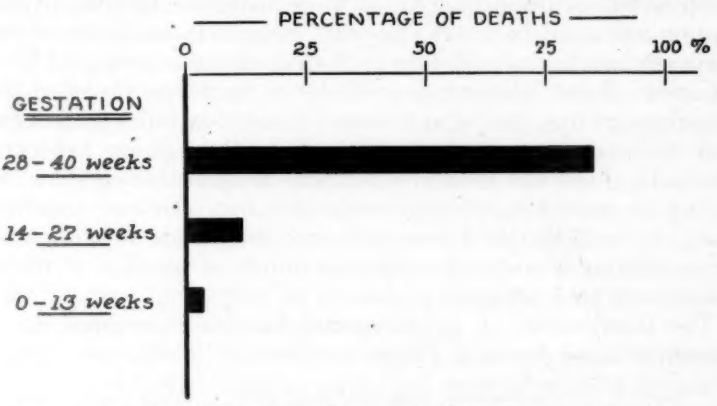

FIG. 2.—Distribution of death with respect to the duration of gestation.

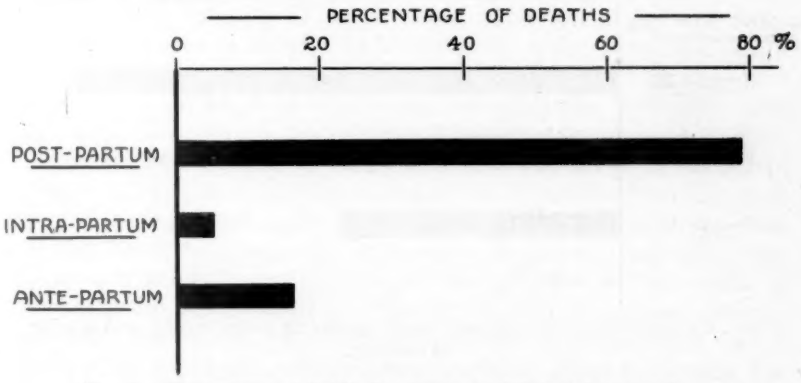

FIG. 3.—Percentages of deaths in pregnancy, labor and puerperium.

it did not usually take place while the patients were gravid. Forty-eight (79%) of the fatalities followed delivery. Furthermore, 23 of these fatalities occurred in the first 24 hours postpartum. Therefore in our series, the first postpartal day is the most critical period of the childbearing act for these women. In contrast to this, the period of labor was relatively benign, since only 3 (5%) of the fatalities occurred at this time. That normal labor, at least in the first stage, does not critically increase the work of the heart, was further suggested by the fact that we found little evidence of increasing cardiac distress during labor. We have emphasized only the first

stage of labor, since the second stage was in most instances extremely short, either because of the normal course of labor or due to prompt operative termination of it.

Relationship of Death to the Cardiac Status. Since the majority of the fatalities in this series occurred following delivery, it seemed advisable to consider them in relation to the condition of the patients immediately before delivery. In most instances, insufficient information was available on the patients' records to enable us to grade their cardiac status according to the classification proposed by the American Heart Association. We have, therefore, classified them into three groups, graded as follows: Grade I includes patients who had maintained cardiac compensation throughout pregnancy; Grade II, those who showed symptoms or signs of congestive heart failure at some time during pregnancy, but who had regained a state of compensation before delivery; and Grade III, those who were suffering from frank congestive failure at the time of the termination of their pregnancy.

The distribution of 44 postpartal fatalities according to our classification is shown in Figure 4. Only 10 (23%) were Grade I

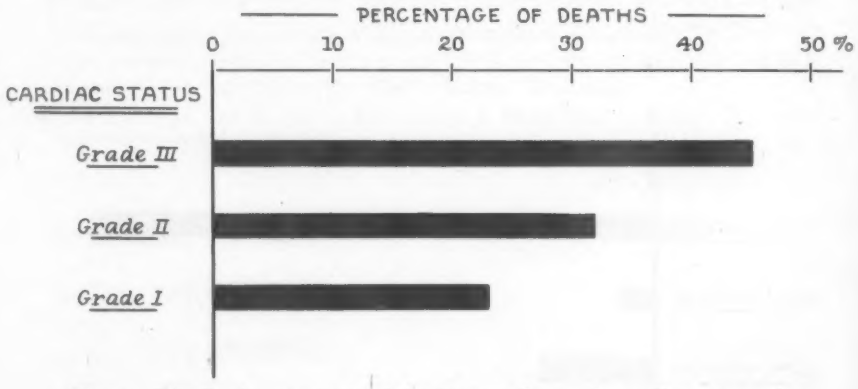

FIG. 4.—Distribution of postpartal deaths according to the cardiac status prior to delivery.

cardiacs, while 14 (32%) were Grade II, and 20 (45%) were Grade III. Moreover, approximately three-fourths of the fatalities in the last group (Grade III) occurred in the first 24 hours postpartum, and were the result of cardiac decompensation. In contrast to this, only one-fifth of the cases in Grades I and II died immediately postpartum. The majority of deaths in these latter two groups were due to delayed congestive failure, to some unavoidable cardiac accident, or to sepsis.

Method of Delivery. Of the 48 patients dying postpartum, 25 were delivered *per vaginam* and 23 by Cesarean section. The majority of Grade III cardiacs were delivered by section while the greater number of Grades I and II fatalities were delivered vaginally. The distribution of the cases according to the manner in which death

occurred and according to the time relationships of death to pregnancy and delivery was, with one exception, similar for the two groups: there was only 1 death from sepsis following vaginal delivery in contrast to 6 following Cesarean section.

Comment. Since, during the decade under consideration, only 61 cases were found which fulfilled the criteria as outlined for this study, it is evident that heart disease, even in a city where rheumatic heart disease is endemic, is not a frequent cause of maternal mortality. It is equally clear, however, that every gravid woman with organic heart disease represents a potential fatality from her cardiac lesion and therefore requires special care and consideration during her pregnancy.

The results of this study confirm, in general, the findings of previous investigators. The fatalities were principally due to congestive heart failure following delivery at or near term. If there is to be a significant decrease in the maternal death rate among cardiac patients who are permitted to attempt childbearing, it must come through a prevention of congestive failure.

The prevention of congestive heart failure prior to delivery is largely a problem in prenatal care. It means bringing each patient to delivery in the best possible cardiac status. The prevention of congestive failure and death after delivery is directly related to this status at the time of delivery. This is illustrated by our data, wherein it has been shown that almost 50% of the postpartal fatalities occurred among women who were decompensated at the onset of labor or at the time when termination of the pregnancy was undertaken.

Most of the fatalities occurred after the 35th week of gestation. This is probably not to be explained by the stress of advancing pregnancy, *per se*, since Cohen and Thomson[1] have shown that the cardiac burden imposed by pregnancy decreases after this time. Moreover, from this study the burden of labor or the strain of operation did not seem to be critical. Even among those patients bordering on congestive failure prior to labor or operation, death or signs of increased cardiac distress seldom appeared during the actual labor or delivery. Confirmatory evidence for this observation has been furnished by Hamilton and Thomson,[5] Irving,[7] and Gorenberg and McGleary,[3] all of whom have noted that congestive failure rarely occurs during labor, and implied that labor usually does not critically increase the work of the heart. On the other hand, Stander[9] and Jensen[8] believe that "labor carries a real danger of congestive failure to the cardiac patient." This moot question deserves further study.

Our data suggest that emptying the uterus is the primary factor precipitating death. This concept is supported by the following: First, the largest percentage of deaths from congestive failure in any 24-hour period occurred in the first 24 hours following delivery, a period during which usually no other primary factor excepting the

physiologic readjustment of the circulation has had time to exert its effect. This relationship held true irrespective of the type of delivery or the cardiac status at the time of delivery. Second, the histories of some of these patients stated that there was a definite, and at times dramatic, increase in cardiac distress occurring promptly following delivery.

A number of hypotheses have been proposed to explain the mechanism of this phenomenon. We favor the concept that the emptying, and subsequent contraction of the uterus, forces blood from the large uterine vessels and sinuses into the general circulation. This autotransfusion seemingly cannot be properly distributed by a damaged heart and congestive failure may result. Nearly 30 years ago Hirst[6] wrote, "The most dangerous period (in the pregnancy of the patient with valvular heart disease). . . . is just after expulsion of the child, when the circulation is much disordered and an extra quantity of blood is thrown back upon the heart." We are aware of no investigations wherein this clinical observation has been tested. On the basis of this hypothesis, Hirst recommended venesection—a procedure which appears to be entirely reasonable. Hamilton and Thomson[5] have tried the effect of applying tight abdominal binders immediately after delivery. The rationale for this was to improve venous circulation by augmenting the respiratory excursions of the chest walls and the diaphragms. Since we have not had personal experience with either of these procedures; we are content to present them without recommendation, *pro* or *con*.

From a study of fatalities alone, such as ours, we can make no definite statement concerning the relative merits of delivery *per vaginam* or by Cesarean section. It is evident that the typical cardiac death may follow Cesarean section as well as vaginal delivery. The incidence of fatal sepsis following Cesarean section, however, is much higher than that following vaginal delivery. Hamilton,[4a] Danforth,[2] and more recently Gorenberg and McGleary[3] have emphasized the dangers of sepsis and other complications following delivery of the cardiac patient by section. In view of these facts, and since the cardiac burden imposed by labor did not appear to be critical, it would seem that vaginal delivery is the method of choice for the majority of cardiac patients uncomplicated obstetrically.

It is likely that the mortality rate due to rheumatic heart disease complicating pregnancy can be lowered. From this study certain recommendations seem justified: It is necessary to bring the patients to delivery in the best possible condition. This can be done by early recognition of the heart disease; strict supervision of the patient's activities by both an obstetrician and cardiologist; and the prompt recognition and treatment of congestive heart failure. Immediate therapy of intercurrent infection, and hospitalization prior to expected delivery are useful measures. Partial digitalization prior to delivery is probably a wise precaution. It seems advisable,

furthermore, to defer delivery, if possible, while the patient is decompensated, and in general to deliver her by the vaginal route. Postpartum, signs of decompensation must be anticipated, and treatment promptly instituted if they appear. Since intravenous fluids may precipitate congestive failure, they should be avoided, particularly within the first 24 hours postpartum.

Summary. 1. Sixty-one maternal deaths due to rheumatic heart disease in Philadelphia during the past decade have been studied in reference to their preventability, manner of death and certain factors influencing the deaths.

2. Analysis of the manner in which death occurred among the cases studied indicated that the fatalities due to this disease resulted principally from congestive heart failure following delivery at, or near term.

3. Of the factors influencing death, the most important one amenable to control was the cardiac status of the patient at the time of delivery. Since this is almost solely dependent upon prenatal care, a significant decrease in the number of maternal deaths due to rheumatic heart disease can only be attained through an improvement in this care.

Acknowledgment is made of the valuable assistance rendered by Dr. Mary M. Livezey in reviewing hospital records for us.

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THE RECOGNITION OF VIRUS TYPE PNEUMONIA.

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This report consists of a survey of 52 cases which have been diagnosed by clinical means as "virus type pneumonia." The condition is a distinct disease entity and it is becoming evident that a

concept of the main features of this type of pneumonia is a valuable asset in the diagnosis and treatment of pulmonary disease.

In general hospital experience various types of pneumonias are encountered—pneumococcus, tuberculous, hemolytic streptococcus, staphylococcus, Friedländer's bacillus and B. tularense and so on. Another interesting and rather common form of pneumonia has been previously described and designated by many different anatomic terms. Our experience with the clinical recognition of virus type pneumonia dates back to 1938 following the report by Reimann[14] of a respiratory disease characterized in some instances by pneumonia and by recovery of a pneumonotropic virus.

This variety of pneumonia, and its differing aspects from other more well known and readily classified pneumonias, has attracted considerable attention. Endemics of this respiratory disease have been reported since 1935, when Bowen[2] recorded his observations on 89 cases of pneumonitis occurring among the troops stationed in Hawaii. The disease was mild and characterized by leukopenia, cough, spotty shadows in Roentgen Ray, few physical signs other than râles and without identifying organisms in the sputum. The author represented the occurrence of pneumonitis to be a complication of influenza. Another report of a similar nature was published by Allen[1] from Fort Sam Houston. It is interesting to note that by purely inductive reasoning Dr. Allen postulated the etiologic agent to be a virus. Accounts of outbreaks at Oregon State College[11] and Cornell University[17] have been published and call attention to the ease of transmission of the disease.

Reimann,[14] previous to these latter reports, described a similar disease of considerably more severity than that elsewhere reported. Eight cases of tracheobronchopneumonia, consisting of patients who became very ill with dyspnea, cyanosis, rather prolonged fever and marked sweating, were described. Reimann also pointed out that in some cases the clinical course was biphasic, so that it might in this respect resemble psittacosis. The character of the disease suggested to him that the etiologic agent was a virus. In a later report Reimann and Havens[15] discussed 407 cases of acute respiratory disease of which 25 presented pneumonia and were more severely ill than those with tracheobronchitis. Interesting descriptions of the clinical aspects of this disease were published in 1940 by Kneeland and Smetana[7] in New York City, where 52 cases with 1 death were observed, and also by Longcope[9] who encountered 32 cases with 2 deaths during an outbreak at Baltimore.

The chief obstacle facing investigation of the etiology of this disease has been in the finding of laboratory animals which regularly exhibited pneumonia after intranasal inoculation with throat washings. In 2 of Reimann's first group of cases Stokes, Kenney and Shaw[18] obtained results in experimental production and serial passage of pneumonia in ferrets. Later, Reimann reported indiffer-

ent results using a similar technique in 11 of the cases from the 1939 epidemic. Weir and Horsfall[21] repeated inoculation experiments, using ferrets as well as a great many other animals without success in demonstrating pathogenicity until they used the mongoose. This animal was shown to be very susceptible to the virus and convincing serial passage was reported. Eaton, Beck and Pearson[3] obtained different animal inoculation results but again showed a virus from cases of atypical pneumonia. Not only do these three separate investigations indicate a virus agent for this type of pneumonia but they also reported dissimilarity to other standard virus strains. Filter-passing differences and varying animal pathogenicity may possibly suggest the existence of more than one strain of a pneumonotropic virus capable of producing a distinct clinical type of pneumonia in humans.

The confusion in the literature of this type of atypical pneumonia is no wise lessened by the numerous anatomically descriptive names: "Acute Diffuse Bronchiolitis,"[10] "Acute Interstitial Pneumonitis,"[17] "Acute Pneumonitis,"[12] "Atypical Pneumonia,"[3,12] "Bronchopneumonia,"[6,8,9,11] "Disseminated Focal Pneumonia,"[16] "Influenzal Pneumonitis,"[2] "Benign Bronchopulmonary Inflammation,"[13] and others.

The protean character of the disease as to the type of cellular reaction within the respiratory system is suggested by the variety of descriptive names mentioned. While awaiting additional proof of the etiology of the disease, the name applied is less important than its clinical recognition as a disease entity. The varieties of pulmonary involvement do not permit an anatomic designation, whereas many features consistently present justify the designation virus type pneumonia.

This report is not a review of old hospital records to include cases of atypical pneumonitis with the intent of re-analysis. Only such cases are included as have come under our observation since 1938, within a period following Reimann's first report. The disease is becoming more common and is frequently being encountered. In this 34-month period at the Henry Ford Hospital in respect to in-patients, this condition was seen almost one-fifth as often as pneumococcus pneumonia. In the last 6 months, from April to October, the proportion of virus type pneumonia to pneumococcus pneumonia has been approximately as 6 to 7.

Seventy-nine cases have been recognized as definitely belonging to this group. Our experience is described in reference to only 52 consecutive cases where the period of observation and the absence of history of preëxistent respiratory disease renders the facts more suitable of analysis.

For convenience, the cases may be divided into three groups: 25 were mildly ill, 17 moderately ill, and 10 severely ill. Chart 1 summarizes certain features of one of the first cases recognized as suffering from this disease. Although the patient was critically ill,

leukocytosis was not present during the first week, and bradycardia was persistent. Repeated sputum examinations revealed no penumococcus on direct typing and only commensal organisms were noted on sputum culture.

In previous reports the mild character of the disease was frequently stressed. Of the 52 patients here reported there were 10 who became seriously ill, 4 of whom showed an illness of critical proportions.

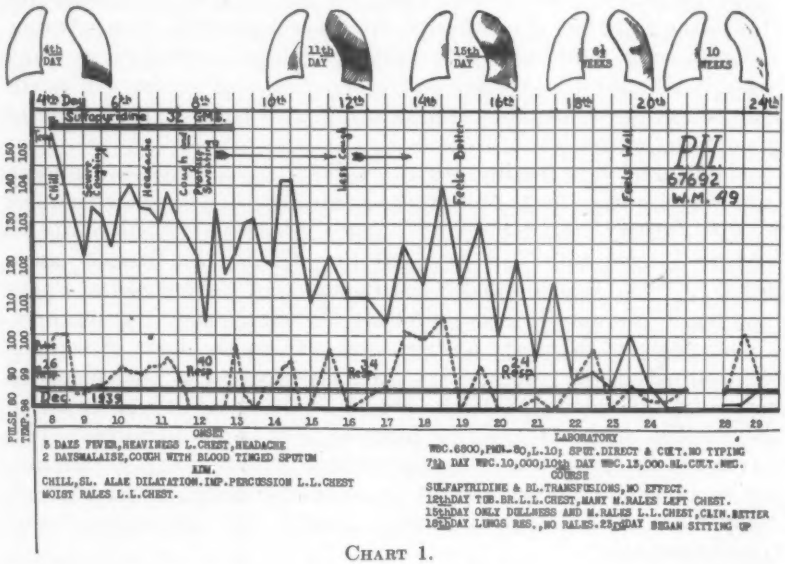

CHART 1.

The disease was, generally speaking, noted in young adults previously in good health. The average age of the group was 27.7, the oldest patient being 52 and the youngest 9; 50% occurred in the decade from 21 to 30.

The *onset* was generally insidious and was marked by the development of a cough which eventually became productive and was associated with some discomfort in the chest. Chilliness occurred in those more severely ill, but frank chills were encountered in only a few instances. Headache, while not always present at the onset, often became an important feature and assumed distressing proportions after the second or third day of the disease. Malaise and anorexia were present in a minor degree, but either or both were marked in about one-third of the patients. Two individuals in whom joint pains were salient complaints were initially suspected of having rheumatic fever.

Mucopurulent sputum, either white or yellowish, was most frequently mentioned; pink sputum containing small streaks of blood or even large amounts of red blood was also noticed. Only 3 patients

described rusty sputum. In almost one-fourth of the cases no sputum was present in significant amounts.

By the time the patients appeared at the hospital, usually on the fourth or fifth day, a variable degree of fever (100° to 103°) was present in all mild or moderate cases. In severely ill cases the temperature frequently was more elevated (103° to 105°). All patients who came under observation early in their illness, on the first to the third day, had rather low temperature elevations regardless of the later serious proportions which the disease assumed. More than half of the patients exhibited a striking relative bradycardia. Over three-fourths of the patients failed to have rapid respiration at the time of their appearance at the hospital generally on the fourth or fifth day.

The chest findings on admission even as late as the fourth or fifth day often were insignificant and generally lagged behind roentgenologic changes. Often slight suppression in breath sounds was the only presenting feature of the chest examination. Moist or sibilant râles were elicited ordinarily at the end of inspiration in many of the patients entering observation when their disease was more established. As the disease increased in severity for a variable number of days more chest findings appeared. Abundant moist type râles were present in almost every case; if not at the onset, they appeared as the disease reached its maximal proportions. Increasing impairment on percussion and suppression of breath sounds appeared later in many cases. Tubular or bronchial breathing occurred infrequently, generally being limited to the severely ill patients.

The *fever* showed certain definite characteristics in almost every case. The temperature varied widely in 24-hour periods and as the disease reached the maximal stage, the lowest temperatures each day approached the normal level. Very few cases showed high plateaus of fever. In most cases the admission temperature was quite elevated except in patients who entered early in the course of the disease. Fever was out of proportion to the general appearance and presenting signs. In frequent instances before the development of physical signs, blood cultures, Widal tests, and other blood agglutinations were obtained because of the marked disproportion between the relatively high fever and low pulse. With the progress of chest developments and as the temperature began to fluctuate to lower limits the pulse became proportionately faster. The duration of fever varied in the 3 groups of cases: in mild cases 10.6 days, in moderate cases 16.2 days and in severe cases 29 days.

Generally speaking, the *chest findings* of râles and dullness became maximal as the temperature began to show lower fluctuations. Remissions of severe proportions occurred in about one-half of the very ill patients. There were no complicating infections observed either in the upper or lower respiratory tract.

While the patients remained under observation in the *postfebrile period*, the physical signs in the chest tended to persist for relatively long periods. Bronchiolar congestion with moist râles was the feature. Actual bronchial breathing, dullness, or on the other hand absence of chest findings, were encountered only in a small number of patients. During this stage of the disease there was little malaise or anorexia corresponding to that seen in influenza.

Laboratory Data. The *white blood count* in 55% of the cases was below 8000 on admission; higher counts were observed in a small number, in some instances possibly related to the more advanced stage in the evolution of the disease when medical aid was sought. Neutrophil percentages were also within normal range in the early days of the illness. In almost all cases the white blood count trend was initially up and later down to normal. The differential count occasionally showed a moderate left shift.

Sputum typing performed at least twice in most of our cases both by the Neufeld method and by inoculation of mice, seldom revealed penumococci.

Sputum showed no significant identifiable organisms. Such commensals as non-hemolytic streptococci, Strep. viridans, Micr. catarrhalis, rarely pneumococci, diphtheroid bacilli and occasionally staphylococci were cultured. In many of the moderately and severely sick patients sputum cultures were repeated at intervals to ascertain the presence of possible secondary pyogenic invaders. The frequency with which reports were returned showing "no growth" or "very few organisms present" deserves comment.

Blood cultures were obtained at least once in each case and were never positive.

Urinalyses showed a transient 1+ or 2+ albuminuria in a relatively small number of the more severely ill patients. Hematuria of varying degree has been observed in a few cases.

In 6 instances electrocardiograms were obtained because of the presence of gallop rhythm. Three patients, all severely ill, showed abnormalities. In 2 instances T-wave abnormalities occurred in Leads II and III. These changes were interpreted as possibly reflecting increased cardiac strain.

One of these individuals, a woman aged 50, had an extensive pulmonary involvement in both lungs as shown by physical examination and Roentgen ray. Dyspnea and cyanosis were marked and the febrile period was very prolonged. A remission occurred 5 weeks following initial subsidence of fever. During both primary and secondary periods of fever the patient was described by different observers as being "almost moribund." Recovery progressed very slowly.

In a second instance, also in an older individual, after dense consolidation had occurred in both lower lobes, and during the height of his illness with high fever and tachycardia, a transient pericardial friction rub was observed. Serial electrocardiograms showed a pro-

longed PR conduction which subsequently returned to normal several weeks after the clearing of all symptoms and signs of his illness except for delayed resolution in both lower lobes.

Pleural effusion was proven to have occurred in 2 instances and the fluid was sterile on culture. In each case the fluid was clear and light amber colored and contained only a few lymphocytes and polymorphonuclear leukocytes. Because of clinical signs suggesting fluid, thoracenteses were performed in 3 other instances but no fluid was obtained.

Roentgen Ray Changes. Excellent descriptions of the variety of Roentgen ray changes which may be found have been published by Kornblum and Reimann,[8] Kneeland and Smetana,[7] and by Longcope.[9] Our cases exhibited the various types of Roentgen ray changes referred to by these authors. In general, the milder cases presented lesser amounts of infiltration than sicker individuals. The type of Roentgen ray change included small patchy densities, fine hazing often involving half of a lung field, a widespread miliary infiltration or a dense area occupying a portion of the lung and corresponding in appearance to "lobar pneumonia." The areas seen in the lung showed a tendency to migrate to new locations on the same side or to the opposite side. In almost one-half of the patients both sides of the chest were ultimately involved. In the initial stages when the infiltration involved the apical region only, differentiation from early tuberculous exudation was impossible. In one patient (Case 2) a pneumothorax was begun before further developments regarding her clinical course and later information relating to contact with an established case of this disease came to light.

In milder cases Roentgen ray densities were transient; in severely ill individuals the appearance of widespread floccular lesions or heavy density persisted for surprisingly long intervals.

The duration of positive Roentgen ray changes showed remarkable parallelism when compared with degree of morbidity.

MINIMUM DURATION OF ROENTGEN RAY CHANGES.

(1)	25	Mild cases	Average 9 days	Limits 3–21 days
(2)	17	Moderate cases	Average 17.3 days	Limits 10–43 days
(3)	10	Severe cases	Average 47 days	Limits 15–90 days

The accompanying table illustrates in a general way the various Roentgen ray features presented by these cases.

ROENTGEN RAY FEATURES.

Bilateral	23
Unilateral migratory	12
Apical infiltration	7
Diffuse miliary or floccular	4
Lobar density	10

Several chest Roentgen rays are presented from 4 cases illustrating some of the roentgenographic features of this disease.

Incubation Period. In accord with other reports the incubation periods noted were from 10 to 26 days in 6 instances where there were definitely known exposures; the average period was 18.7 days. The details of these exposures indicate that the disease is readily transmissible. In one instance a patient (S. S., a psychiatric department nurse) visited her sister (O. S) only once during the latter's hospitalization. Sixteen days later the nurse became ill and eventually was admitted to the hospital where her disease assumed serious proportions.

Source. Thirty-seven of the cases occurred in patients drawn from other than institutional sources, while 10 cases have occurred

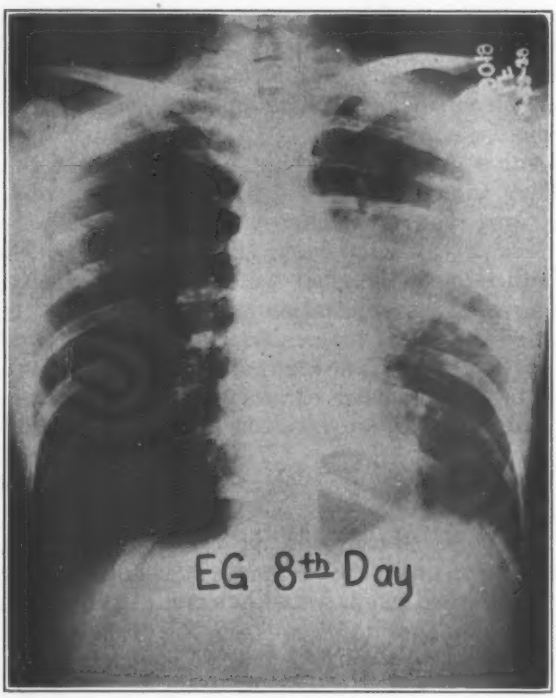

FIG. 1 (Case 1).

among hospital personnel and 5 cases from among patients transferred from the "sick bay" at the River Rouge Naval Service School to this hospital. It is evident that this disease is no longer limited to institutional outbreaks involving younger age groups.

Discussion. This group of cases is presented without any direct evidence that a virus was the causative organism. As has been pointed out above, investigation of the virus agent has been carried out by a number of workers. Prior recovery of a virus from similar cases and the absence of significant findings in sputum or blood

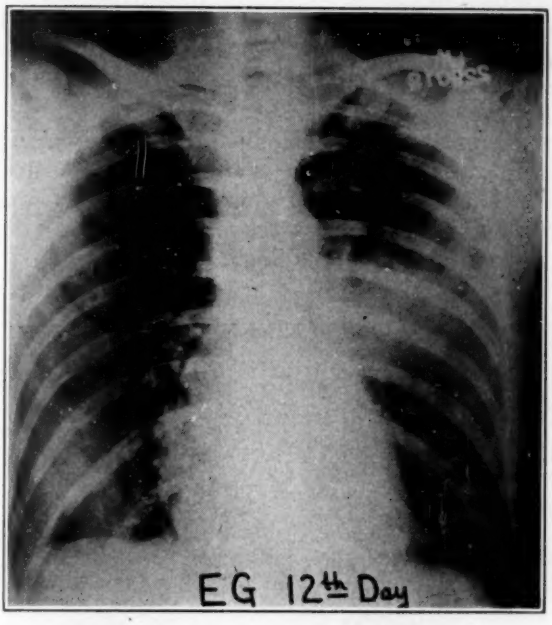

FIG. 2 (Case 1).

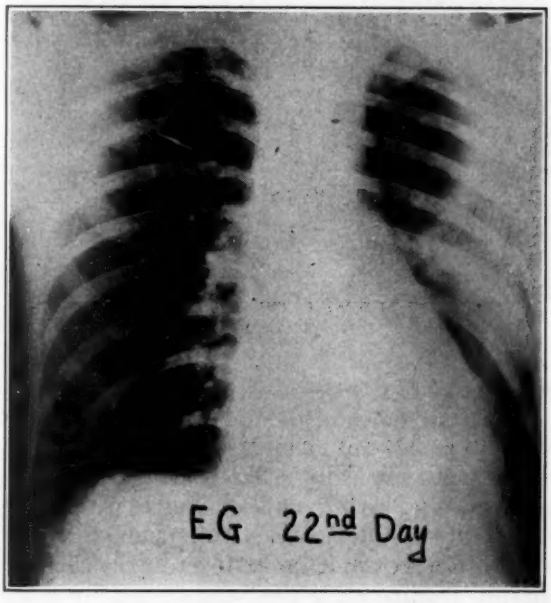

FIG. 3 (Case 1).

favor a non-bacterial etiology. Certain resemblances to other virus diseases in reference to course, length of incubation period and ease of transmission suggest the virus nature of this disease.[14] The term "virus type pneumonia" for this form of respiratory disease appears warranted.[4]

The diagnosis pneumococcus pneumonia[20] is receiving wider usage now that more exact bacteriologic analysis has been introduced and it is probable that the designations lobar or bronchopneumonia may be less often applied. These latter names may remain as useful terms in roentgenology and pathology.

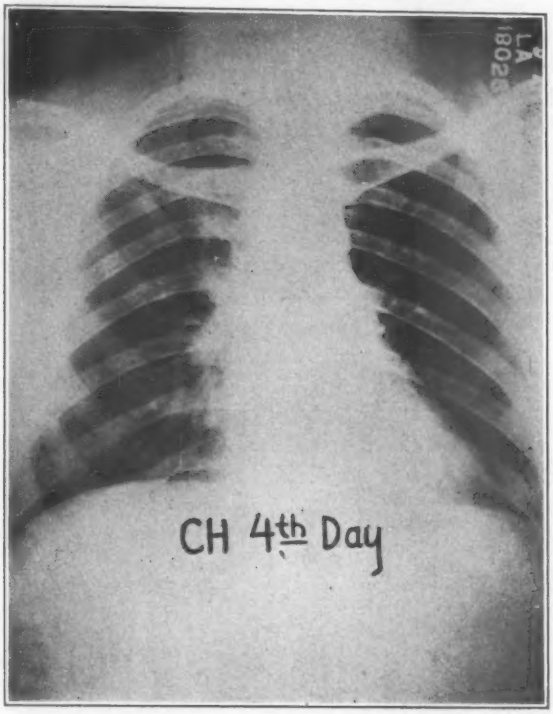

FIG. 4 (Case 2).

Prompt recognition of this disease is important in order to prevent institution of possibly harmful therapeutic measures, or their continuation when obviously not helpful. In most instances, a positive diagnosis can be made clinically. The history of an insidious onset featured by headache, cough and chilliness with mucopurulent sputum and some aching pain in the chest is characteristic. Temperature and pulse disproportion with fever of considerable degree having a sharply fluctuating course and falling by lysis is also a contributory feature in diagnosis. Generally the alæ do not dilate;

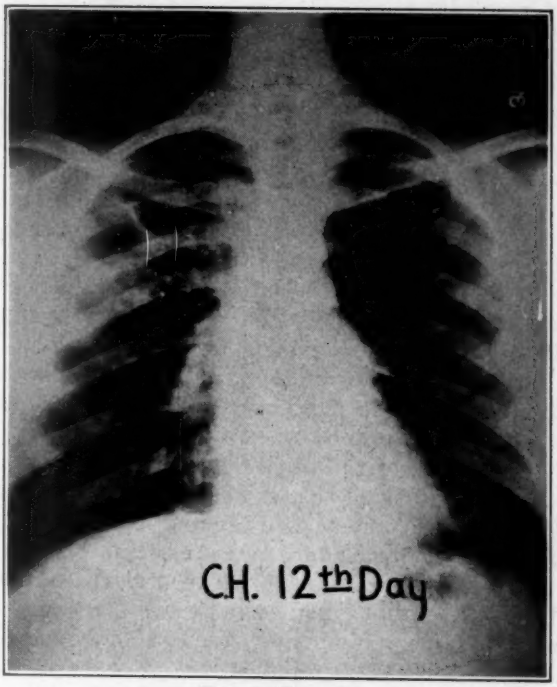

FIG. 5 (Case 2).

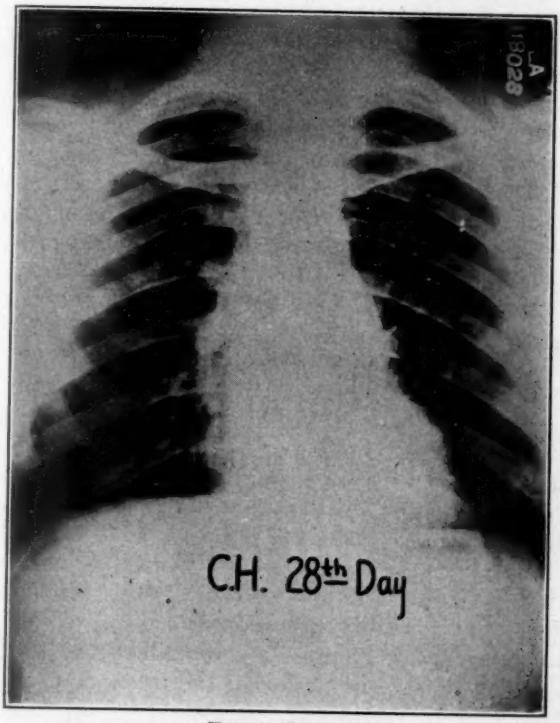

FIG. 6 (Case 2).

there is no cyanosis within the first 4 to 5 days but there may be considerable later. Distention of the abdomen and liver congestion are absent. There is no pleural pain of the type seen in pneumococcus pneumonia; instead there is an aching in the chest which may or may not be influenced by respiration. Even on the third or fourth day chest findings are insignificant in proportion to the degree of fever, generally there are a few râles late in inspiration or suppression of breath sounds. Initial chest roentgenograms are often not abnormal but later as more chest findings appear may reveal infiltration. The sulfonamide drugs are without effect in treatment. In doubtful cases where initially the diagnosis may be in question, a trial of these drugs may further help in establishing the diagnosis. As yet we know of no definite laboratory test that gives positive evidence of the disease except methods designed to recover the virus itself from throat washings, and for best results this probably should be done within the first 3 days of the illness.[19]

In regard to treatment, the only measures definitely indicated are symptomatic. Blood transfusions have been given to a number of our severely ill patients but there has been no constant response. Sulfonamide drugs, including sulfapyridine, sulfathiazole, and sulfadiazine, have not shown any indications of value in treatment. Neoarsphenamine has been tried in 3 cases without results sufficiently promising to deserve comment. Oxygen may be administered where dyspnea or cyanosis exist in significant degree, preferably by tent with admixture of intercurrent use of carbon dioxide.

Only 4 deaths have been reported to date. One of these occurred in association with involvement of the central nervous system. The 2 fatalities reported by Longcope occurred in individuals having mitral stenosis. The increasing frequency of the disease and the rather large number of patients in this group that were seriously ill suggest that deaths may become more numerous. It is not probable that deaths will be related to the harmful effects of secondary invaders such as occurred in the influenza pandemic. Longcope has stated that this disease, which has been differentiated from influenza, appears to increase the resistance of the patient to pyogenic organisms.[9] Our experience supports this statement.

Francis[5] and other workers have observed a high antibody titer in respect to influenza type A during the third decade of life. All reports of virus type pneumonia have stressed the occurrence of the disease principally in this same age group. In the future it may be found that antibody titers for this virus differ sharply from those of influenza A virus.

The increasing incidence and severity of virus type pneumonia indicate a rising virulence of the etiologic agent. In epidemic or pandemic form the mortality rate would be expected to increase, especially in the older age group. It is probable such deaths would result from failure of the circulation in the presence of widespread

FIG. 7 (Case 3).

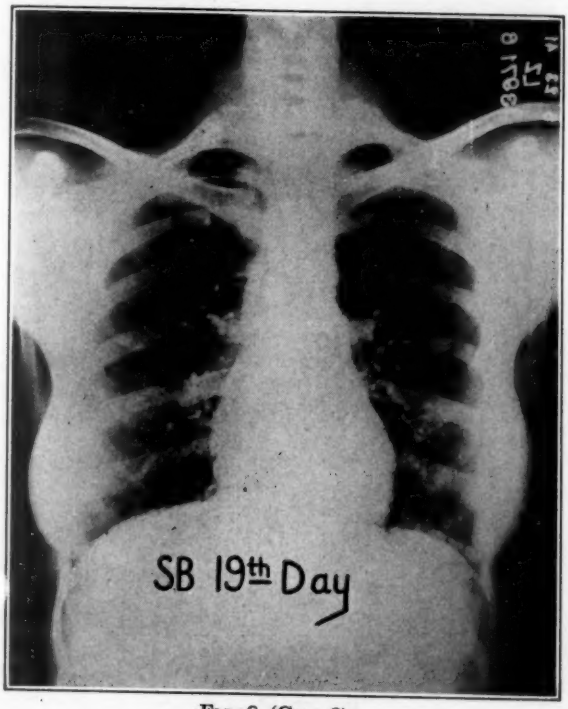

FIG. 8 (Case 3).

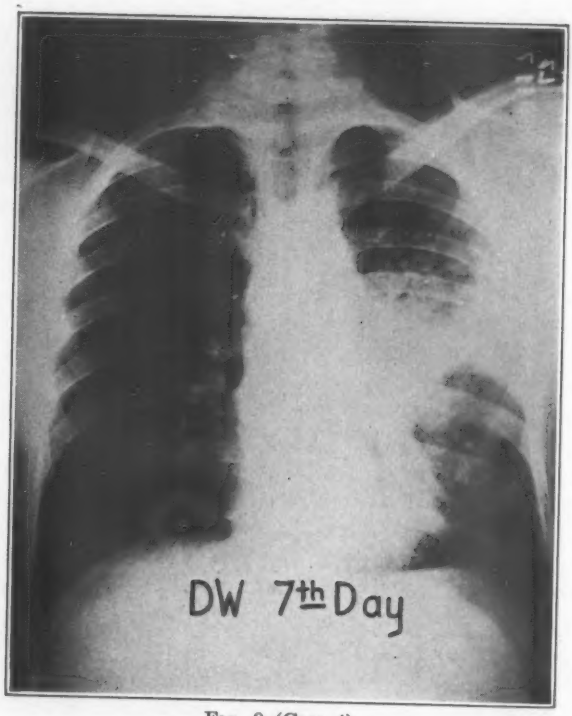

FIG. 9 (Case 4).

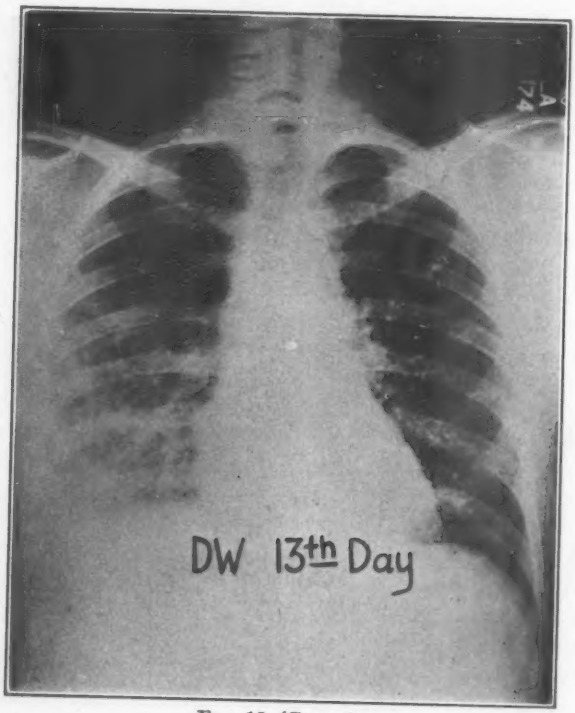

FIG. 10 (Case 4).

pulmonary changes, which changes have been encountered already in some patients.

TABLE 1.—DIFFERENTIATING CRITERIA IN THREE TYPES OF PNEUMONIA.

	Pneumococcus.	Virus type.	Influenza.
Incubation	1–2 days	2–3 weeks	1–4 days
Onset	Abrupt	Insidious	Abrupt
Symptoms	Chill	Chilliness	Repeated chills
	Pleural pain	Headache	Aching
Cough	Loose	Dry	Loose
Sputum	Rusty	Mucoid	Bloody
Appearance	Toxic	Not toxic	Markedly toxic
Dilatation alæ	+	0	+
Herpes	Frequent	Rare	Infrequent
Heart rate	Rapid	Slow (50%)	Slow at times
Respiratory rate	Elevated	Normal	Normal
Distention	Frequent	None	Variable
Fever	Maintained	Hectic	Remittent
Chest findings:			
Impairment	Early	None or late	Infrequent
Tubular breathing	Frequent	Rare and late	Infrequent
Râles	Variable	Moist (end of inspiration)	Fine crackling
Sputum	Pneumococci	Occas. higher type	B. influenza often
	Direct typing	Pneu. culture	Streptococcus
WBC	High	Normal	Low
Roentgen ray	Dense consolidation	Often bilateral lobular (lobar and miliary at times)	Variable diffuse Lobular
Treatment	Response to chemotherapy	No response	For secondary invaders
Pyogenic complications	Not frequent	None	Very frequent

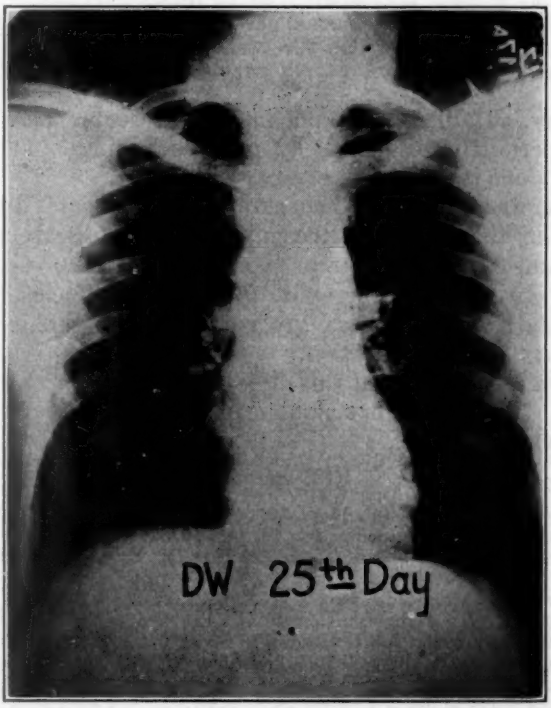

FIG. 11 (Case 4).

CASE 1. E. G., nurse, aged 30, 14 days after exposure, began having symptoms of headaches, cough and fever and 6 days later entered the hospital. Temperature 104.2°. White blood count 5100. Râles were audible in left upper and there was slight impairment on percussion. Infiltration in left upper appears on the eighth day. Involvement in right lower showed on the twelfth day. Ten days later no Roentgen ray shadow remains on the right. Pneumothorax which had been begun after an initial diagnosis of acute exudative tuberculosis was discontinued. Recovery occurred.

CASE 2. C. H., staff physician, aged 27, 23 days after exposure was admitted in the second day of headache, dry cough, and malaise. On the fourth day of his illness examination and chest Roentgen ray were essentially negative. White blood count 6800. Temperature was 101°. Soon after the appearance of râles in the right upper a chest film on the twelfth day showed parenchymatous infiltration in the right upper. After other films showed rapid clearing, a final Roentgen ray on the twenty-eighth day was clear.

CASE 3. S. B., 21-year-old girl, was admitted on eighth day of illness consisting principally of cough, fever, malaise and aching in both sides of the chest. Temperature on admission 102.4°. White blood count 7850. Chest Roentgen ray on admission (eighth day) showed dense consolidation in both lower lung areas. Physical examination revealed mainly dullness and râles bilaterally in lowers. Another film on the nineteenth day showed a moderate amount of infiltration remaining.

CASE 4. D. W., 28-year-old Naval ensign, entered hospital on seventh day with cough, severe sweats and fever. White blood count 18,050. Temperature 99.2°. Chest examination revealed râles in left upper. Chest Roentgen ray showed consolidation in the mid-portion of the left lung. Six days later a film showed fine nodular appearance simulating hematogenous spread of tuberculosis. On the twenty-fifth day the lung fields were almost clear.

Summary. 1. Virus-type pneumonia presents specific clinical features permitting diagnosis by positive findings. Diagnosis by exclusion alone is seldom necessary.

2. Chemotherapy with the sulfonamide group of drugs is not indicated in this disease. Recognition of this disease may avoid needless and possibly dangerous therapeutic efforts.

3. The initial roentgenographic appearance may closely simulate acute exudative tuberculosis. Progress roentgenographic study may be necessary for differentiation.

4. There is evidence that this disease is now showing an increasing incidence. This fact is not alone explained by familiarity with the clinical concept.

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SULFADIAZINE IN PNEUMONIA.

TREATMENT IN 239 CASES.*

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Sulfadiazine (2-sulfanilamido-pyrimidine) is the latest member of the sulfonamide group to be given extensive clinical trial in the treatment of pneumonia. Sulfapyridine was the first of these drugs to show a striking therapeutic effect in pneumonia, but from the start the almost universal occurrence of nausea following sulfapyridine militated against its use. Sulfathiazole was the next sulfonamide drug to have extensive use in pneumonia, and while there was less nausea and vomiting following its administration, there were other evidences of greater toxicity and, in addition, the clinical

* This investigation has been conducted under a grant of the Josiah Macy, Jr. Foundation. The sulfadiazine was supplied by Lederle Laboratories, Inc.

response was not quite as certain as with sulfapyridine. Consequently, many physicians felt more secure in continuing to use sulfapyridine in the treatment of pneumonia in spite of the bothersome gastric symptoms which are produced. The data that are accumulating from the trial of sulfadiazine would indicate that: 1, it has a protective value at least equivalent to that of sulfapyridine; 2, it causes little or no nausea and vomiting; and 3, there is a low incidence of other toxic reactions.

In August, 1940, Roblin, Williams, Winnek, and English[9] reported upon the synthesis and chemistry of sulfadiazine. In December, 1940, Feinstone and his associates[2] described their experimental studies on the toxicity, absorption, and chemotherapeutic activity of this new sulfonamide drug. Their experiments in animals indicated that: 1, the blood levels of sulfadiazine were higher than those of the other sulfonamide drugs because of differences in absorption and excretion; 2, the degree of acetylation of sulfadiazine was less than of sulfapyridine; 3, the acute and chronic toxicity was lower than that of sulfapyridine and sulfathiazole; 4, sulfadiazine had a high therapeutic activity against pneumococcal, streptococcal, staphylococcal, and Friedländer's bacillus infections in mice.

These experimental advantages have been borne out by clinical trial. Plummer and Ensworth,[6] Reinhold, Flippin, Schwartz, and Domm,[8] Peterson, Strauss, Taylor, and Finland,[5] and Sadusk and Tredway[10] have reported findings that indicate: 1, with a given dosage, because of differences in absorption and excretion, higher blood levels are obtained with sulfadiazine than with sulfapyridine or sulfathiazole; 2, sulfadiazine acetylates to a lower degree than sulfapyridine; 3, the incidence of clinical toxicity is low. Reinhold, Flippin, Schwartz and Domm showed also that sulfadiazine enters the peritoneal, pleural, and cerebrospinal fluids more readily than sulfathiazole. More recently Flippin, Rose, Schwartz and Domm[4] have compared their experience with sulfadiazine in the treatment of 100 cases of pneumonia with a similar experience with sulfathiazole. Their findings showed again higher blood levels of sulfadiazine, and also less acetylation with this drug. In addition, their figures show a slightly lower mortality rate, a slightly more rapid clinical improvement, and a lower incidence of toxic reactions with sulfadiazine than with sulfathiazole. Finland, Strauss and Peterson[3] have reported the successful use of sulfadiazine in a number of infections, including pneumonia, with infrequent toxic reactions. Dowling, Hartman, Sugar and Feldman[1] have reported favorably on the use of sulfadiazine in pneumococcic pneumonia.

The present report represents our clinical findings in 239 patients with pneumonia treated with sulfadiazine at Bellevue Hospital during the winter of 1940–41. These cases were part of an alternate series being carried out in order to ascertain the relative efficacy of sulfonamide drugs alone and sulfonamide drugs combined with

serum in the treatment of pneumonia. However, since this study has already been reported[7] and because it reveals no appreciable difference* between the fatality rate in the chemotherapy-alone cases and the chemotherapy-and-serum group, such a division in this report seems unnecessary. Only cases of pneumococcus pneumonia are included. The majority of the cases fall into the classification of lobar pneumonia, but a few might be called bronchopneumonia. The sulfadiazine was administered orally in most of the cases and the usual dosage was 2 gm. initially and then 1 gm. every 4 hours. All cases had routine sputum typing and one or more blood cultures. Frequent determinations of sulfadiazine level in the bood were made, as well as blood counts, urinalyses and Roentgen rays. An initial blood non-protein nitrogen determination was obtained in each case.

Effect on Fatality Rate. Table 1 shows the cases distributed according to pneumococcal type and lists the deaths in the total group as well as in the bacteremic group. In the total series of 239 cases, there were 26 deaths (a fatality rate of 10.9%). Eight of the 26 deaths occurred in less than 24 hours after treatment was commenced, and with these excluded there remained 231 cases with 18 deaths (a mortality of 7.8%). Of the 239 cases, 42 (17.4%) were bacteremic, and of these, 13 (30.9%) died. The fatal cases were distributed quite evenly through the different types. While there were 33 Type III cases in the series, there were only 3 fatalities (9.1%). The most striking record was obtained in Type II pneumonia. Forty-two patients were of this type, and there were only 3 deaths, 2 of which occurred less than 24 hours after treatment was started. Thirteen of the 42 Type II cases showed bacteremia and all but 2 of these recovered; 1 of these 2 was a 24-hour fatality. The Type I group contained 44 cases with 4 deaths (1 of which was a 24-hour death) and 10 bacteremias with 3 deaths (1 of which was a 24-hour death). The temperature chart of our most remarkable patient is shown in Figure 1.

* Of the 113 patients who fell into the serum-plus-sulfadiazine group, 67 actually received serum, the rest having marked improvement by the time the typing was completed. Of these 67 cases, 16 were Type I; 17, Type II; 9, Type III; 5, Type IV; 2, Type V; 6, Type VII; 2, Type VIII; and 10 were higher types.

The results in the present series of 239 cases show a moderate difference in fatality rates in favor of sulfadiazine-plus-serum treatment, 9 of 113 patients (7.9%, or excluding 24-hour deaths, 5.5%) in this group having died. Of the 126 sulfadiazine-only cases, 17 died (13.5%, or excluding 24-hour deaths, 9.9%). In view of the comparatively limited number of sulfadiazine cases, however, the significant figures in our alternated series study are those obtained by adding the present cases (less 51 cases included previously) to those already reported. This gives the following final figures for our alternated series:

	Cases.	Deaths.	
Drug only	403	47	(11.66%)
Drug plus serum	392	48	(12.24%)
Eliminating 24-hour deaths:			
Drug only	393	37	(9.41%)
Drug plus serum	376	32	(8.51%)

TABLE 1.—DISTRIBUTION OF CASES AND BACTEREMIAS AND RESULTS BY TYPES.

Type.	Cases.	Deaths.	24-hr. deaths.	Bacteremias.	Deaths.	24-hr. deaths.
I	44	4	1	10	3	1
II	42	3	2	12	1	1
III	33	3	0	3	1	0
IV	14	1	1	2	1	1
V	10	1	0	3	0	0
VI	5	1	0	1	1	0
VII	30	3	2	4	2	1
VIII	14	3	0	5	2	0
IX	3	1	0	1	1	0
XI	1	0	0	0	0	0
XII	1	0	0	0	0	0
XIII	2	1	0	0	0	0
XIV	6	1	0	0	0	0
XV	4	1	0	0	0	0
XVI	1	0	0	0	0	0
XVII	3	0	0	0	0	0
XVIII	2	0	0	0	0	0
XIX	2	0	0	0	0	0
XX	5	0	0	0	0	0
XXI	1	0	0	0	0	0
XXII	4	1	1	1	1	1
XXIII	1	0	0	0	0	0
XXV	2	0	0	0	0	0
XXIX	4	0	0	0	0	0
XXXIII	5	2	1	0	0	0
Total	239	26 (10.9%)	8	42	13 (30.9%)	5
Excluding 24-hr. deaths	231	18 (7.8%)	..	37	8 (21.6%)	

E. S.: A married woman of 27 was admitted to Bellevue Hospital with a history of cough and pain in the left chest for 2 days, and expectoration of bloody sputum for 1 day. She was 7 months' pregnant. Signs of consolidation were present over the left upper lobe. The sputum yielded Type I pneumococcus. The blood culture showed innumerable colonies of the same organism. The leukocyte count was 11,600 per c.mm. Sulfadiazine therapy was started at once and she improved rapidly, but on the fifth day of illness she went into labor and delivered a 2-pound 3-ounce baby, who lived for 22 hours. Her temperature, after having been normal for 2 days, began to rise on the seventh day of illness. (See Fig. 1.) She developed a leukocytosis of 40,000 per c.mm. and signs of fluid at the left base and a chest tap on the ninth day yielded 12 cc. of a thin, cloudy fluid, which was positive for Type I pneumococci on culture. Signs of fluid persisted but no fluid was secured by thoracentesis on the eleventh day. In view of her subsequent excellent progress and regression of physical and Roentgen ray signs no further chest taps were attempted and she was discharged in good condition on the thirty-second hospital day after an uneventful convalescence.

Cases Treated Early Compared With Those Treated Late. Division of the cases according to when sulfadiazine therapy was commenced is made in Table 2. Two groups are shown: 1, early (treatment started during the first 3 days); 2, late or uncertain (treatment commenced on the fourth day or later, or duration of illness not ascertainable but usually of considerable length). Of the 108 patients who were treated early, only 7 died (6.5%) (1 24-

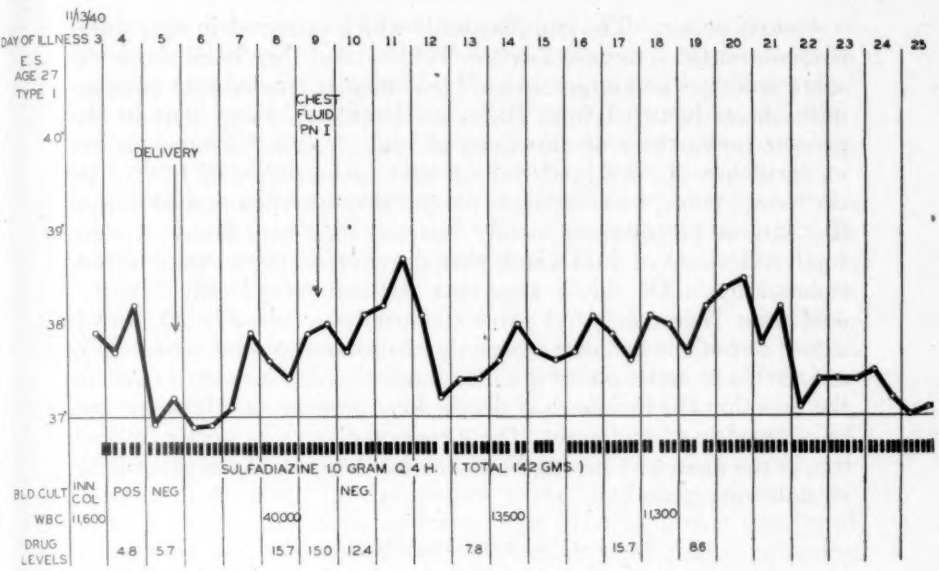
11/3/40
DAY OF ILLNESS 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25
E. S.
AGE 27
TYPE I
CHEST FLUID PN I
DELIVERY
40°
39°
38°
37°
SULFADIAZINE 1.0 GRAM Q 4 H. (TOTAL 142 GMS.)
BLD CULT INN. COL. POS. NEG. NEG.
WBC 11,600 40,000 13,500 11,300
DRUG LEVELS 4.8 5.7 15.7 15.0 12.4 7.8 15.7 8.6

FIG. 1.—Data of patient E. S. with pneumonia, positive blood and pleural fluid cultures, and pregnancy.

hour death is excluded). The late or uncertain cases showed a fatality rate of 8.9% (7 24-hour deaths excluded).

TABLE 2.—DISTRIBUTION AND RESULTS ACCORDING TO DURATION OF ILLNESS BEFORE ADMISSION TO HOSPITAL.*

	Cases.	Deaths.	Fatality rate (%).
Early (first 3 days)	108	7	6.5
Late or uncertain	123	11	9.0

* 24-hour deaths not included.

Relation of Age of Patients to Outcome. While the mortality of 7.8% in 231 cases of pneumonia (excluding 24-hour deaths) treated with sulfadiazine is highly creditable, the results are more remarkable when cases are distributed by the age of the patient (Table 3). Among the 27 patients under 30 years of age, there were no deaths. In the 30 to 50 years group, 86 cases occurred with but 1 death (1.2%). Thus in 113 cases under 50 years of age, there was only 1 death or a fatality rate of 0.89% (24-hour deaths excluded). In the group over 50 years of age there were 118 patients, with 17 deaths (14.4%), excluding 24-hour deaths.

TABLE 3.—DISTRIBUTION OF CASES AND RESULTS BY AGE.

	Cases.	Deaths.	Fatality rate (%).
Under 30	27	0	0
30 to 50	86	1	1.2
50 and over	118	17	14.4
Total	231	18	7.7

* 24-hour deaths not included.

Complications. The complications which occurred in this sulfadiazine-treated series are listed in Table 4, and they have about the same incidence as a larger series of pneumonias treated with sulfonamide drugs reported from Bellevue Hospital,[7] except that in the present series there are no cases of lung abscess. Empyema has an incidence of 3.3% and endocarditis an incidence of 1.2%. Of the 8 empyemas, 1 was a simple pleural effusion when tapped during life, but at postmortem cloudy infected fluid was found; 2 were small collections of fluid which were discovered only on postmortem examination. Of the 5 empyema patients who lived, 2 recovered after thoracotomy, 1 after thoracenteses (see Fig. 1), and 2 signed out of the hospital before thoracotomy could be done. It is reasonable to assume that if sulfonamide therapy is started early in the infection the incidence of deaths from serious complications can be reduced to a low figure. The 3 endocarditis cases were admitted late in the disease, 1 having been sick for 7 days and the other 2 for an indefinite period.

TABLE 4.—COMPLICATIONS (239 CASES).

	Cases.	Deaths.
Empyema	8	3
Otitis media	5	0
Pleural effusion	5	0
Pneumococcus endocarditis	2	2
Meningitis and empyema	1	1
Pneumococcus endocarditis and empyema	1	1
Otitis media and pleural effusion	2	1
Pericardial effusion	1	1

Toxic Reactions. In spite of the fact that the blood levels (usually 7 to 9 mg. per 100 cc.) during sulfadiazine therapy were higher than those obtained with either sulfapyridine or sulfathiazole, the incidence of toxic reactions was lower (Table 5). Of the 239 total

TABLE 5.—TOXIC REACTIONS (239 CASES).

	Cases.
Nausea and vomiting:	
Before and during treatment	2
Only during treatment	3
Leukopenia	4
Anemia	1
Drug rash and fever	4
Drug fever	2
Microscopic hematuria	4
Renal colic and gross hematuria*	1
Temporary partial deafness	1

* Since this paper was written, further experience with a larger number of cases has shown that renal toxic reactions occur in about 5% of cases.

cases, only 5 vomited and 2 of these had vomited before admission as well as afterwards. Leukopenia occurred in 4 patients; it was of moderate degree in each case and disappeared when the drug was discontinued. There were no instances of agranulocytosis. Anemia, also of moderate severity, was encountered once. There were 4 cases of drug rash with fever, and 2 cases of drug fever. Microscopic

hematuria was found in 4 instances, and renal colic with hematuria occurred in 1 case. One patient had a temporary partial deafness which may have been caused by the drug. In addition, there were several patients who showed temporary mental disturbances during treatment, but nearly all of these patients were chronic alcoholics, and we were unable to decide just what the relative rôles of the alcoholic state, the pneumonia, and the sulfadiazine were; hence we have not listed them. It is likely, however, that the drug was, at least in part, responsible in several cases.

Preëxisting Disease in the Fatal Cases. The incidence of serious preëxisting disease among the 26 patients who died was high. Eight had hypertensive and arteriosclerotic heart disease, and of these, 3 were alcoholics. Two had diabetes mellitus, and 1 of these was in diabetic acidosis. One patient had asthmatic bronchitis, 1 had chronic nephritis and was in uremia on admission, and 1 had acute lymphogenous leukemia. It is our feeling that these preexisting diseases contributed greatly to the fatal outcome. In addition, 1 patient convalescing from Type III pneumonia developed symptoms and electrocardiographic changes suggestive of acute myocardial infarction and died suddenly.

Summary and Conclusions. 1. Sulfadiazine has been used in the treatment of a group of 239 patients with typed pneumococcus pneumonia.

2. The fatality rate was 10.9% (7.8%, if 24-hour deaths are excluded).

3. There was only 1 death among the 113 patients who were under 51 years of age (1 24-hour death is excluded).

4. The number of complications of the disease was small.

5. The incidence of toxic reactions was low.

6. Sulfadiazine appears to have about the same degree of effectiveness as sulfapyridine and sulfathiazole in the treatment of pneumococcus pneumonia, and at the same time causes fewer toxic reactions.

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THE ABSORPTION, EXCRETION AND DISTRIBUTION OF 2-SULFANILAMIDOPYRAZINE (SULFAPYRAZINE) IN MAN.*

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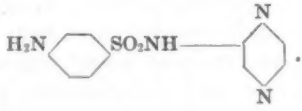
2-Sulfanilamidopyrazine ("sulfapyrazine"), the para-isomer of sulfadiazine, was synthesized in 1941 by Ellingson.[2] Preliminary studies[3,4] have indicated that its toxicity for man and animals is relatively low, and that its antipneumococcal activity is high.[3,6] In the present communication, we wish to report studies upon the absorption, excretion and distribution of sulfapyrazine and of sodium sulfapyrazine in man.

Properties of Sulfapyrazine Compounds. The structural formula of sulfapyrazine is



Sulfapyrazine and acetylsulfapyrazine are tasteless white powders, whose solubilities in 100 cc. of water at 37° C. are: sulfapyrazine, 5.2 mg.; acetylsulfapyrazine, 5.6 mg. The pH of sodium sulfapyrazine in 10% aqueous solution is 9.3.[2]

Plan of Study. *Absorption of Sulfapyrazine.* Blood levels[1] were determined at frequent intervals after single 4 gm. oral doses of sulfapyrazine powder, sulfapyrazine tablets, and sodium sulfapyrazine powder. In addition, many determinations were made on treated patients receiving 1 gm. every 4 or 6 hours. Also, the absorption of sulfapyrazine and sulfadiazine was compared at different times in the same subject.

Convalescent patients on a routine ward diet, with no apparent disease of the gastro-intestinal tract or of the cardiorenal system were used for single dose absorption curves. Their average fluid intake was about 2 liters a day. Powdered drug or crushed tablets were given, before breakfast, suspended in about 300 cc. of water.

* This study was aided by a grant in honor of Craig Yeiser and by a grant from Mead Johnson & Co.

Excretion of Sodium Sulfapyrazine. Four grams of sodium sulfapyrazine monohydrate dissolved in 100 cc. of distilled water were administered intravenously, during 20 to 30 minutes, to normal males, and blood levels determined at frequent intervals. The 24 hour urinary output of 4 of these subjects was collected for 3 or 4 days. In others, the concentration of sulfapyrazine in cerebrospinal fluid obtained from the lumbar sac was compared with that of simultaneously drawn blood, at various times over a 12 hour period. Whenever a local anesthetic was required in obtaining specimens of body fluids, ethyl chloride was used.

Results. ABSORPTION OF SULFAPYRAZINE. Four to 8 hours after the oral ingestion of 4 gm. of sulfapyrazine, an average maximum blood level of about 2.7 mg. per 100 cc. is attained. Chart 1 shows that this peak may be reached as early as 2 hours or as late as 12, and that about 1 mg. per 100 cc. is still present in the blood

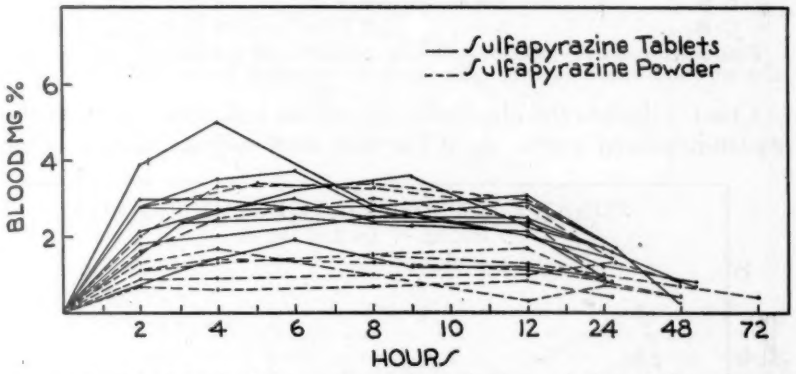


CHART 1.—Blood levels of free sulfapyrazine following a single oral dose of 4 gm Each curve represents a separate subject.

after 24 hours. Drug given as powder did not appear to be quite as well absorbed as drug incorporated into tablets. No correlation between size of dose and body weight was found through the range of 50 to 75 mg. per kilo.

When the initial dose of 4 gm. is followed by 1 gm. every 4 hours, blood levels of about 6 mg. per 100 cc. free sulfapyrazine and 8 mg. total sulfapyrazine are usually maintained (Table 1).* These are

TABLE 1.—SULFAPYRAZINE LEVELS IN PATIENTS UNDER TREATMENT.

Dosage.	No. of observations.	Highest level recorded in any patient (mg./100 cc.).	Lowest level recorded in any patient (mg./100 cc.).	Median of all levels recorded (mg./100 cc.).
1 gm. every 4 hours:				
Free	67	16.5	2.0	6.5
Total	61	21.2	3.1	8.1
1 gm. every 6 hours:				
Free	73	11.5	0.6	4.7
Total	66	12.9	0.9	5.6

* Blood level determinations in the early sulfapyrazine-treated patients[3] were performed in the general clinical laboratory of the hospital by substitute technicians. It is believed that these levels were probably lower than the levels actually attained and are not included in this table.

comparable to the levels maintained by 1 gm. of sulfadiazine every 6 hours.[5] When the initial 4 gm. dose of sulfapyrazine is followed by 1 gm. every 6 hours, average blood levels of 4 to 5 mg. per 100 cc. are maintained. Similarly the maximum blood level following a single oral dose tends to be lower for sulfapyrazine than for sulfadiazine. Table 2 compares the absorption of the two drugs in the same subject at different times.

TABLE 2.—COMPARISON OF MAXIMUM BLOOD LEVEL ATTAINED BY SULFAPYRAZINE AND SULFADIAZINE IN THE SAME SUBJECT.

	Free.		Total.	
Subject.	Sulfapyrazine (mg./100 cc.).	Sulfadiazine (mg./100 cc.).	Sulfapyrazine (mg./100 cc.).	Sulfadiazine (mg./100 cc.).
M. B.	2.5	3.8	3.2	4.6
Q. W.	3.1	5.6	3.7	6.1
F. B.	3.0	5.5	4.0	6.3
C. H.	2.8	2.8	3.4	3.0

Figures represent the highest blood level recorded after a single oral dose of 4 gm. The interval between the administration of the two drugs was at least 5 days.

Chart 2 depicts the absorption of sodium sulfapyrazine from the gastro-intestinal tract. As is the case with sodium salts of other

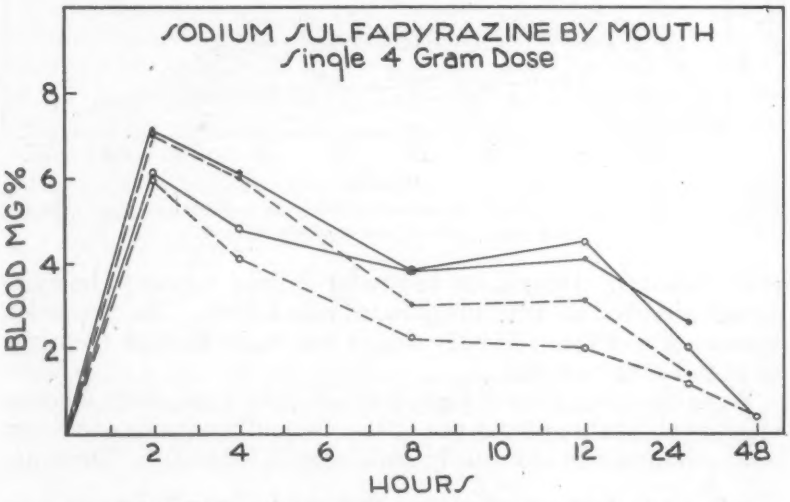


CHART 2.—Blood levels following sodium sulfapyrazine by mouth, in 2 subjects. Dotted lines represent "free" levels; solid lines "total" levels.

sulfonamides, sodium sulfapyrazine is absorbed more rapidly and attains higher blood levels than the acid drug.

BLOOD LEVELS FOLLOWING INTRAVENOUS SODIUM SULFAPYRAZINE. Four grams of sodium sulfapyrazine monohydrate were administered intravenously to 9 subjects and 6 gm. to 1 (Chart 3). Blood levels were determined 4, 8, 12, 24, and 48 hours after the completion of the injection in all individuals, and ½, 1, 2, and 72 hours as well in some.

This compound is excreted rather slowly. At the end of 8 hours, the "free" blood level averaged 6 mg. per 100 cc., and at the end of 12 hours, 3 mg. per 100 cc. Some drug remained in the blood after 24 hours and traces after 48 and 72 hours.

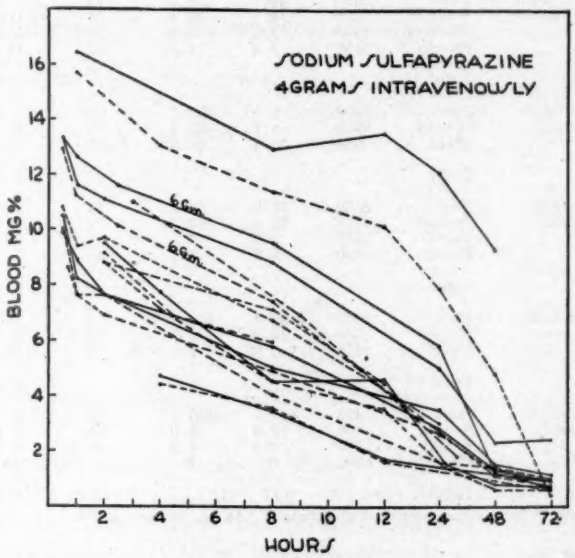


CHART 3.—Blood levels following injection of 4 gm. sodium sulfapyrazine monohydrate (3.44 gm. sulfapyrazine) intravenously. Dotted lines represent "free" sulfapyrazine; solid lines, "total" sulfapyrazine.

RENAL EXCRETION OF SULFAPYRAZINE. Table 3 shows the rate of renal excretion of sulfapyrazine following an intravenous injection of 4 gm. of sodium sulfapyrazine monohydrate. Thirty-five to 50% of the drug is excreted in the first 24 hours. Another 20% to 25% is eliminated in the second 24 hours, and about 5% in the third. The total amount of sulfapyrazine accounted for in the urine was only 70% of that injected. In this respect, the excretion of the drug resembles the excretion of sulfamethylthiazole, as reported by Strauss *et al.*[7]

Subject A. S. was used to compare the excretion of the sodium salts of sulfapyrazine, sulfadiazine and sulfathiazole in the same individual at different times. Sulfathiazole was excreted most rapidly, sulfadiazine less rapidly, and sulfapyrazine most slowly.

No attempt was made to estimate total excretion of the drug by patients receiving it orally. However, many determinations were made on single urine specimens and on 12 or 24 hourly samples. These are summarized on Table 4. The only pertinent fact contained in these data is the great variability of the urinary concentration, which was undoubtedly conditioned by the volume and the

TABLE 3.—RECOVERY OF SULFONAMIDES IN URINE FOLLOWING INTRAVENOUS INJECTION OF 4 GM. OF THE MONOHYDRATE SODIUM SALT.

Subject and age.	Drug.	Period (24 hrs.).	Urine vol. (ml.).	Drug (mg./100 cc.). Free.	Drug (mg./100 cc.). Total.	% recovered drug conjugated.	Administered drug recovered in urine. Gm.	Administered drug recovered in urine. %.
L. H. 18	Sulfapyrazine	First	2200	30.6	58.4	48	1.28	37.3
		Second	2550	14.0	32.8	57	0.84	24.3
		Third	1540	7.2	16.6	57	0.26	7.5
		Fourth	2100	2.9	4.9	41	0.10	2.9
		Total	..	..	..	..	2.48	72.1
E. A. 24	Sulfapyrazine	First	2560	21.0	55.2	62	1.41	40.8
		Second	2570	8.7	33.9	74	0.87	25.5
		Third	935	10.3	24.0	57	0.22	6.4
		Total	..	..	..	..	2.50	72.7
A. S. 47	Sulfapyrazine	First	2580	57.0	66.3	14	1.71	49.7
		Second	1160	48.6	64.2	24	0.75	21.8
		Third	1140	3.9	4.7	17	0.01	0.3
		Fourth	1080	4.4	7.7	43	0.01	0.3
		Total	..	..	..	..	2.48	72.1
A. S.	Sulfadiazine	First	2020	84.1	102.5	18	2.07	60.0
		Second	1700	24.9	45.7	46	0.78	22.7
		Third	1250	6.8	7.7	12	0.10	2.8
		Total	..	..	..	..	2.95	85.5
A. S.	Sulfathiazole	First	995	200.0	260.3	23	2.60	75.5
		Second	600	12.6	18.0	30	0.11	3.2
		Third	1380	2.5	4.6	46	0.06	1.8
		Fouth	1500	0	0	..	..	0
		Total	..	..	..	..	2.77	80.5

4 gm. sodium sulfapyrazine monohydrate contain 3.44 gm. sulfapyrazine.

TABLE 4.—LEVELS OF SULFAPYRAZINE IN 30 RANDOM URINE SAMPLES OF PATIENTS UNDER TREATMENT, 1 GM. EVERY 4 HOURS.

	Free (mg./100 cc.).	Total (mg./100 cc.).	% conjugated.
Median	51	101	53
Highest	185	300	86
Lowest	8	12	20

hydrogen ion concentration of the sample studied. Both sulfapyrazine and acetylsulfapyrazine are many times more soluble in alkaline than in acid urine (Table 5). As is the case with sulfadiazine, the solubility of the acetyl derivative exceeds that of the "free" compound.*

TABLE 5.—SOLUBILITY OF SULFAPYRAZINE AND OF ACETYLSULFAPYRAZINE IN BUFFERED URINE.

Final pH.	Sulfapyrazine (mg./100 cc.).	Acetylsulfapyrazine (mg./100 cc.).
4.5	5.1	5.9
5.0	4.9	5.7
5.5	4.0	8.2
5.8	6.0	13.3
6.3	7.7	25.2
6.7	14.2	77.2
7.1	32.6	127.2
7.4	59.1	136.0

* These studies were carried out by Mr. Robert E. Eakin.

SULFAPYRAZINE IN CEREBROSPINAL FLUID. Simultaneous blood and spinal fluid levels were determined at various intervals in 4 subjects given sodium sulfapyrazine intravenously. Table 6

TABLE 6.—SIMULTANEOUS LEVELS IN BLOOD AND CEREBROSPINAL FLUID IN PATIENTS RECEIVING 4 GM. SODIUM SULFAPYRAZINE INTRAVENOUSLY.

	Blood (mg./100 cc.).		C.S.F. (mg./100 cc.).			Blood (mg./100 cc.).		C.S.F. (mg./100 cc.).		
	Free.	Total.	Free.	Total.	%.	Free.	Total.	Free.	Total.	%.
	2 hours.					4 hours.				
L. T.	8.8	..	0.5	..	5.6					
P. B.	..	..	..	..	..	13.0	..	2.2	..	16.9
G. B.	..	..	..	..	..	4.2	4.7	1.2	1.1	25.3
E. H.	11.0	..	2.1	2.2	19.0					
	8 hours.					12 hours.				
L. T.	7.1	..	1.6	..	25.3	4.2	..	2.1	..	50.0
P. B.	11.4	12.9	3.7	4.4	34.1	10.1	13.5	5.1	6.4	47.4
G. B.	3.5	3.4	1.8	2.0	53.3	1.6	1.7	1.0	1.2	64.2
E. H.	6.7	7.0	3.5	4.1	52.2					

"%" indicates percentage of "free" blood level represented by spinal fluid level.

shows that the sulfapyrazine in the spinal fluid increased gradually until, at the end of 12 hours, its level was 50% to 60% that of the blood level. This ratio is maintained in patients under continuous treatment (Table 7); these patients were free of infection of the central nervous system.

TABLE 7.—SIMULTANEOUS BLOOD AND CEREBROSPINAL FLUID LEVELS IN PATIENTS RECEIVING 1 GM. SULFAPYRAZINE EVERY 4 HOURS.

Patient.	Hours after last dose.	Blood (mg./100 cc.).		C.S.F. (mg./100 cc.).		%	
		Free.	Total.	Free.	Total.	Free.	Total.
C. C.	2.5	2.3	..	1.4	..	60.9	
B. B.	3.0	6.8	..	3.1	..	45.6	
M. P.	3.0	3.1	..	1.1	..	33.4	
W. B.	2.0	10.4	15.3	7.0	7.1	67.3	46.4
E. F.	2.0	8.9	10.7	4.9	5.0	55.0	49.9
J. F.	2.0	12.7	15.9	10.2	10.6	80.3	66.7

"%" indicates percentage of blood level represented by spinal fluid level.

SULFAPYRAZINE IN BODY FLUIDS. Sulfapyrazine reaches concentrations in the pleural and peritoneal cavities approaching and occasionally exceeding that in the blood. A similar observation was made on two samples of synovial fluid, and one specimen of fluid from the anterior chamber of the eye. Smaller proportions of the drug appeared in milk. These data are presented in Table 8.

DISTRIBUTION OF SULFAPYRAZINE BETWEEN PLASMA AND RED BLOOD CELLS. In the blood of treated patients, the concentration of sulfapyrazine in the plasma is approximately double that in the

TABLE 8.—SIMULTANEOUS SULFAPYRAZINE LEVELS IN BLOOD AND VARIOUS BODY FLUIDS.

Patient.	Body fluid.	Dosage, gm.	Hours after dose.	Blood (mg./100 cc.). Free.	Blood (mg./100 cc.). Total.	Body fluid (mg./100 cc.). Free.	Body fluid (mg./100 cc.). Total.	% Free.	% Total.
N. G.	Pleural	4	6	2.3	3.1	3.2	3.5	141	113
H. G.	Pleural	4	7	3.6	7.3	1.9	4.4	53	60
S. S.	Pleural	4	6	5.9	...	2.3	...	39	
J. F.	Pleural	4	2¾	4.1	4.6	3.5	4.0	85	86
E. C.	Pleural	4	6	3.6	4.4	2.4	3.9	66	88
E. B.	Pleural	1q. 4th hr.	3½	14.8	15.6	16.3	18.6	111	118
Q. W.	Pleural	4	8	3.4	4.4	2.4	2.6	72	59
G. F.	Ascitic	4	5	3.1	3.6	4.0	4.3	129	119
G. B.	Ascitic	4	7	2.0	3.4	2.4	2.7	120	79
J. C.	Joint	4	5½	4.0	5.4	7.3	7.9	182	144
P. W.	Joint	4	..	7.4	8.4	7.2	6.7	97	79
M. M.	*Anterior chamber of eye	4	6	2.9	3.8	1.8	3.0	62	80
E. M.	Milk	4	4	3.1	3.7	1.1	..	34	
M. H.	Milk	4	4	6.4	..	1.1	..	17	
C. B.	Milk	4	4	6.0	..	1.1	..	18	
S. S.	Milk	4	4	2.9	3.0	1.1	1.1	37	35
S. S.	Milk	4	8	2.2	3.1	1.0	1.3	45	42
W. B.	Saliva	1q. 4th hr.	2	10.4	15.3	3.5	..	33	
E. O.	Saliva	1q. 4th hr.	2	2.3	2.7	1.2	1.2	52	44

"%" indicates percentage of blood level represented by body fluid level.
* Procaine was used as a local anesthetic.

red blood cells (Table 9). In this respect, the drug resembles sulfathiazole and sulfadiazine, but differs from sulfapyridine and sulfanilamide,[7] which are distributed more uniformly.

TABLE 9.—DISTRIBUTION OF "FREE" SULFAPYRAZINE BETWEEN PLASMA AND RED BLOOD CELLS.

Patient.	Whole blood (mg./100 cc.).	Plasma (P), (mg./100 cc.).	R.B.C. (C), (mg./100 cc.).	P/C.	Hematocrit.
W. B. . . .	5.6	8.3	3.1	2.7	41.5
R. E. . . .	5.9	8.4	4.1	2.0	50.0
W. G. . . .	7.8	10.0	4.4	2.3	
W. G. . . .	8.7	11.1	5.0	2.2	
C. W. . . .	7.4	9.6	5.1	1.9	
E. B. . . .	14.6	18.5	8.5	2.2	
E. B. . . .	14.8	19.4	9.8	2.0	
O. B. . . .	2.0	2.5	1.8	1.4	
J. K. . . .	7.3	10.1	4.2	2.4	

CONJUGATION OF SULFAPYRAZINE. Following single doses, oral or intravenous, the amount of combined sulfapyrazine in the blood never exceeded 25%, though in patients under treatment, the proportion of combined drug was somewhat higher. The median acetylation is about 30% with extremes of 5% and 78%. In urine the conjugated drug usually exceeds 50% of the total drug.

Discussion. The behavior of sulfapyrazine in the human body closely resembles that of its isomer sulfadiazine. It is absorbed rather slowly from the gastro-intestinal tract, and is excreted more slowly by the kidney than are sulfathiazole and sulfapyridine. It seems likely that as glomerular filtrate containing sulfapyrazine passes down the renal tubules, appreciable amounts of the drug are reabsorbed.

Orally administered sulfapyrazine yields lower blood levels on a given dosage schedule than does sulfadiazine. However, the milligram for milligram antipneumococcal activity of sulfapyrazine, as measured by *in vitro* and by mouse curative tests, is considerably greater than that of sulfadiazine.[6] The effective sulfapyrazine blood level, therefore, may be lower than the effective sulfadiazine level.

The danger of damage to kidneys by crystals of poorly soluble sulfonamides like sulfapyrazine and sulfadiazine is just as great with the non-acetylated as with the acetylated form. For, in contradistinction to the other sulfonamides in common use, the conjugated forms of these two drugs are just as soluble as the free forms, at any given pH. Since, however, the solubility of both forms rises sharply with increasing alkalinity, careful attention to the maintenance of alkaline urine should, in clinical practice, keep renal complications at a minimum. It is interesting that in dogs, renal calculi containing 75% "free" sulfapyrazine by weight but no conjugated drug are formed in animals kept on large doses for 2 months.[4]

Summary. In a study of the absorption, excretion and distribution of sulfapyrazine in the human body it was found that:

1. The drug is absorbed rather slowly from the gastro-intestinal tract.

2. It is excreted more slowly by the kidney than is sulfadiazine, sulfapyridine, or sulfathiazole.

3. Acetylsulfapyrazine is more soluble in water or urine than sulfapyrazine. Both compounds are many times more soluble in alkaline than in acid media.

4. Sulfapyrazine enters the cerebrospinal fluid slowly, reaching concentrations of about 50% of that of the blood 12 hours after an intravenous injection.

5. Concentrations of the drug in most body fluids approach or exceed the concentrations in the blood; very little sulfapyrazine appears in milk. However, its concentration in the blood plasma is approximately double that in the red blood cells.

We are indebted to Mr. Walter Pritz, Jr., and to Mr. Richard Goldsmith for aid in carrying out the chemical determinations.

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THE EFFECT OF SULFANILAMIDE ON THE EXPERIMENTALLY DAMAGED LIVER.

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The clinical use of sulfanilamide has been followed in some cases by the development of jaundice. In the majority of instances the jaundice has been hemolytic; in the remainder (about 0.6% of patients who have been treated with sulfanilamide[13]) it has been ascribed to hepatitis.[1,2,3,6,7,13,17,20] Experimentally, the administration of sulfanilamide to rats has not resulted in damage to the hepatic cells that was detectable by ordinary staining procedures.[15] In an attempt to explain why among some patients receiving the drug hepatitis develops and among others it does not, an attractive hypothesis was advanced by Bannick and his associates.[1] They maintained that the reason for its development among some patients was that their livers had been damaged prior to the administration of sulfanilamide and the drug caused the preëxisting hepatic damage to progress to a stage from which regeneration was impossible.

In order to test the foregoing hypothesis experimentally, four different experiments were planned, each devised to determine the effect of sulfanilamide on the already damaged liver or on the liver predisposed to damage by a recognized procedure. Accordingly, sulfanilamide was administered to: 1, a group of animals in which hepatitis had been induced by means of carbon tetrachloride; 2, a group in which hepatitis was being induced by means of carbon tetrachloride; 3, a group receiving alcohol; and, 4, a group in which obstructive jaundice had been induced by ligation of the common duct.

Procedure. Adult male albino rats of an inbred Wistar strain having an average body weight of 308 ±54 gm. were used. The rats were fed a standard commercial stock diet, had access to an ample supply of fresh water and were housed 3 per cage. Those animals given sulfanilamide received it daily by means of stomach tube in the form of a suspension in tap water, or in 20% alcohol in the experiment in which alcohol was administered. The amount of sulfanilamide in all cases was 1 gm. per kilogram of body weight; such a dose has been shown to be toxic.[10,11,14] The animals given carbon tetrachloride were exposed to its fumes in a specially constructed chamber into which air, passed through a bottle of carbon tetrachloride, was forced to enter. The animals were exposed for a period of 30 minutes daily; one such exposure is sufficient to produce a moderate degree of central necrosis extending to and in some instances involving the midzone of the hepatic lobule. Those animals to which alcohol, with or without sulfanilamide was given, received it daily by means of a stomach

tube; the dose given was 6 cc. of a 20% solution. In those animals in which obstructive jaundice had been induced, the common duct had been triply ligated approximately midway between the hilum of the liver and the entrance of the choledochus into the duodenum.

At regular intervals, animals were exsanguinated under light ether anesthesia; the livers were removed and weighed, and portions were fixed in 10% solution of formaldehyde. Sections were stained with hematoxylin and eosin, Sudan IV, the Mallory-Heidenhain stain for connective tissue and Pap's reticulum stain.

Results. *Effect of Simultaneous Administration of Sulfanilamide and Carbon Tetrachloride.* Twelve animals breathed the fumes of carbon tetrachloride for 30 minutes daily until they were killed for necropsy. Six of them also received daily the given amount of sulfanilamide during the entire period. Necropsy was performed on half of the animals at the end of the first week and on the remainder at the end of the second week of the experiment and sections of the livers were fixed for staining.

Necropsies. The livers of both groups of animals necropsied at the end of the first week were enlarged and had prominent lobular markings. Those of the animals that received both carbon tetrachloride and sulfanilamide were dark brown, almost black; while the livers of the animals receiving only carbon tetrachloride were yellow and "nutmeg" in appearance.

Microscopic examination of the livers of those animals that received both sulfanilamide and carbon tetrachloride revealed that the hepatic cells in the central and in portions of the midzones were enlarged. The cytoplasm of these cells stained a faint pink with hematoxylin-eosin, and was vacuolated. The nuclei were pyknotic but centrally placed. The hepatic cells in the uninvolved portions of the lobules appeared normal. There was little or no cellular infiltration in the lobules, and when present, was confined to a narrow portion of the central zone immediately adjoining the central vein (Fig. 1). The sections stained with Sudan IV revealed that the enlarged cells in the central and midzones contained small and large droplets of fat. There was no connective tissue proliferation or condensation and the reticulum pattern was preserved.

The damage was more extensive in the livers of those animals that received carbon tetrachloride only. In a totally irregular manner, small islands of normal hepatic cells were interspersed between larger groups of damaged cells. The latter were enlarged, vacuolated and the affinity of their cytoplasm for the eosin stain varied. The nuclei of these cells were pyknotic but centrally placed. The largest cells contained little or no staining cytoplasm; in some of these only a few faint threads could be seen between a centrally or eccentrically placed pyknotic nucleus and the periphery of the cell (Fig. 2). Some degree of collapse was present about the central vein and in such areas the hepatic cells were replaced by lymphocytes, histiocytes and a few fibroblasts. In the sections especially stained these areas of collapse contained only a few connective tissue

fibers but there was a moderate amount of condensation of reticulum. In the sections stained with Sudan IV many fat droplets of varying size were present only in those enlarged cells which were vacuolated in the sections stained with hematoxylin-eosin.

At the end of the second week, the gross appearance of the livers of both groups of animals was similar to that at the end of the first week, except that the lobular markings of the livers of those animals that received only carbon tetrachloride were more prominent. Microscopic examination again revealed that the livers of those animals that received both sulfanilamide and carbon tetrachloride were less damaged than the livers of the animals that received carbon tetrachloride only. In the sections of the livers of the former, the hematoxylin-eosin stain revealed that the damage to the hepatic cells was not confined to the central zone of the lobules but also occurred in other zones. The pattern of the damage was less regular than at the end of the first week, this being due to regeneration of some of the cells in the inner zones of the lobules. The damaged cells were enlarged and were either vacuolated or else contained only a few fine granules or threads between an eccentrically placed pyknotic nucleus and the periphery of the cell (Fig. 3). The enlarged vacuolated hepatic cells contained stainable fat but the large pale ones did not. There was no connective tissue proliferation although there was some cellular infiltration present in the areas of collapse immediately adjoining the central veins. In such areas there was a slight amount of condensation of reticulum. The reticulum framework was disintegrated in the areas occupied by the large pale cells.

The sections of the livers of the animals treated with carbon tetrachloride alone revealed changes in the hepatic cells similar to those observed at the end of the first week. However, the degree of central collapse was greater and there was a greater degree of cellular infiltration. These cells again consisted of lymphocytes, histiocytes and a few fibroblasts. Similar cellular elements extending in bands from the central areas toward the periphery of the lobules gave the sections the appearance of an early cirrhosis without cirrhosis actually being present (Fig. 4) as the Mallory-Heidenhain stained sections revealed only a few fibers of connective tissue. Instead the bands contained many entwined reticulum fibers. In the sections

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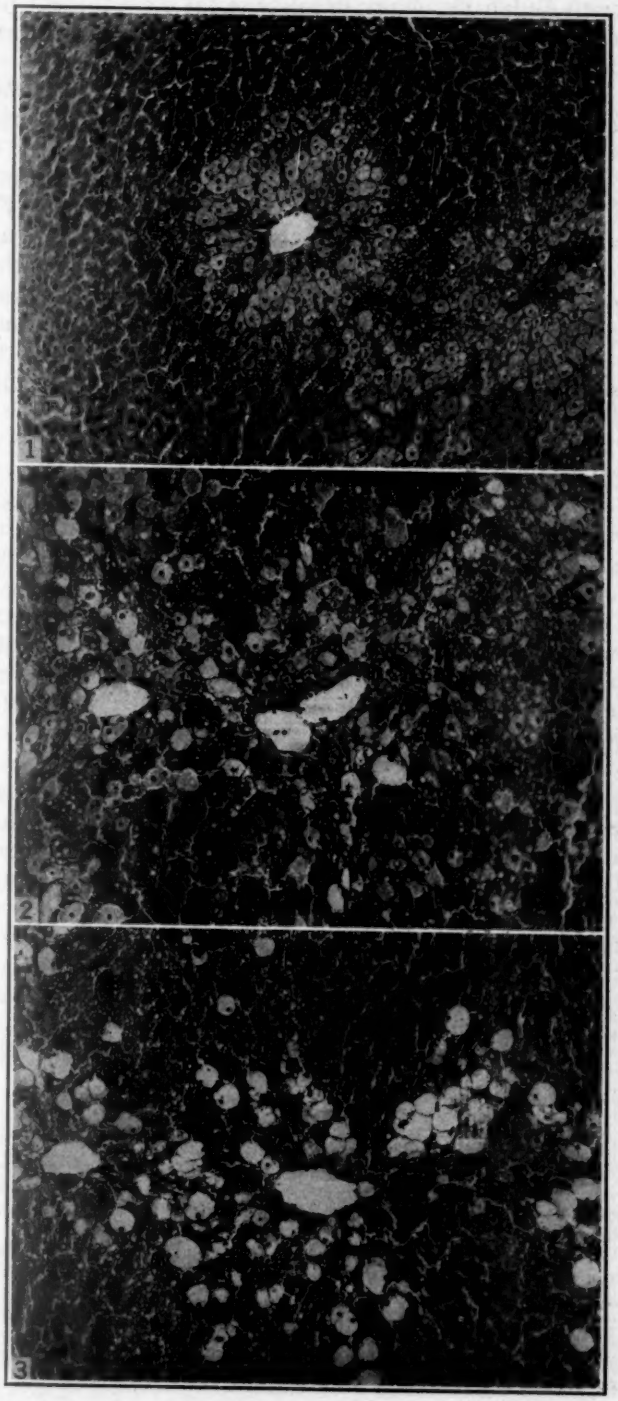
LEGENDS FOR PLATE ON OPPOSITE PAGE.

FIG. 1.—Liver of rat that received sulfanilamide and inhalations of carbon tetrachloride daily for 1 week. The cells about the central vein are enlarged and vacuolated. The nuclei are pyknotic (H and E, × 100).

FIG. 2.—Liver of rat that received only inhalations of carbon tetrachloride daily for 1 week. The damage is more extensive and there is a greater degree of cellular infiltration than in the section in Figure 1, though the exposure to carbon tetrachloride was exactly similar in the 2 instances (H and E, × 100).

FIG. 3.—Liver of rat that received sulfanilamide and inhalations of carbon tetrachloride daily for 2 weeks. The most severely damaged cells are the large pale ones with eccentrically placed pyknotic nuclei (H and E, × 100).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stained with Sudan IV, many droplets of fat were present only in those enlarged cells which were vacuolated in the sections stained with hematoxylin-eosin.

Effect of Sulfanilamide Following Damage by Carbon Tetrachloride. Fifteen animals were exposed to fumes of carbon tetrachloride for 30 minutes daily for 1 week. Necropsy was performed on 3 of the animals at the end of this time and portions of the livers were removed for microscopic examination. Hepatic damage (Fig. 2) was present. The remaining 12 animals were divided into two equal groups. Sulfanilamide was given daily to one group until the animals were killed for necropsy, while the remaining group of 6 animals served as controls. Necropsy was performed on 3 animals from each group at the end of the first and the second week, respectively, following discontinuance of administration of carbon tetrachloride.

Grossly there was no difference in the appearance of the livers of these two groups, except for the darker color of the livers of the group which received sulfanilamide. Examination of microscopic sections did not reveal any evidence of central necrosis or deposition of fat in either group at either period, indicating that hepatic regeneration had occurred satisfactorily in both groups. Administration of sulfanilamide had not impeded regeneration (Fig. 5).

Effect of Alcohol and Sulfanilamide Administered Simultaneously. Eighteen animals received 6 cc. of a 20% solution of alcohol daily by means of stomach tube. Half of these animals (*i. e.*, 9) received sulfanilamide in addition to the alcohol. Necropsy was performed on 3 animals from each of the two groups at the end of the second, the third and the fourth week respectively, of the experiment.

Examination of sections of livers of both groups of animals did not reveal any evidence of damage of hepatic cells, of proliferation of connective tissue or of interruption of the reticular framework. Some of the hepatic cells at the periphery of the lobules in animals which received only alcohol contained droplets of fat (Fig. 6) but such deposition of fat did not occur in the livers of the group which received the sulfanilamide also.

Effect of Sulfanilamide on the Liver in Obstructive Jaundice. To 9 of 18 animals in which the common ducts had been ligated, sulfanilamide was administered daily until the animals were killed for

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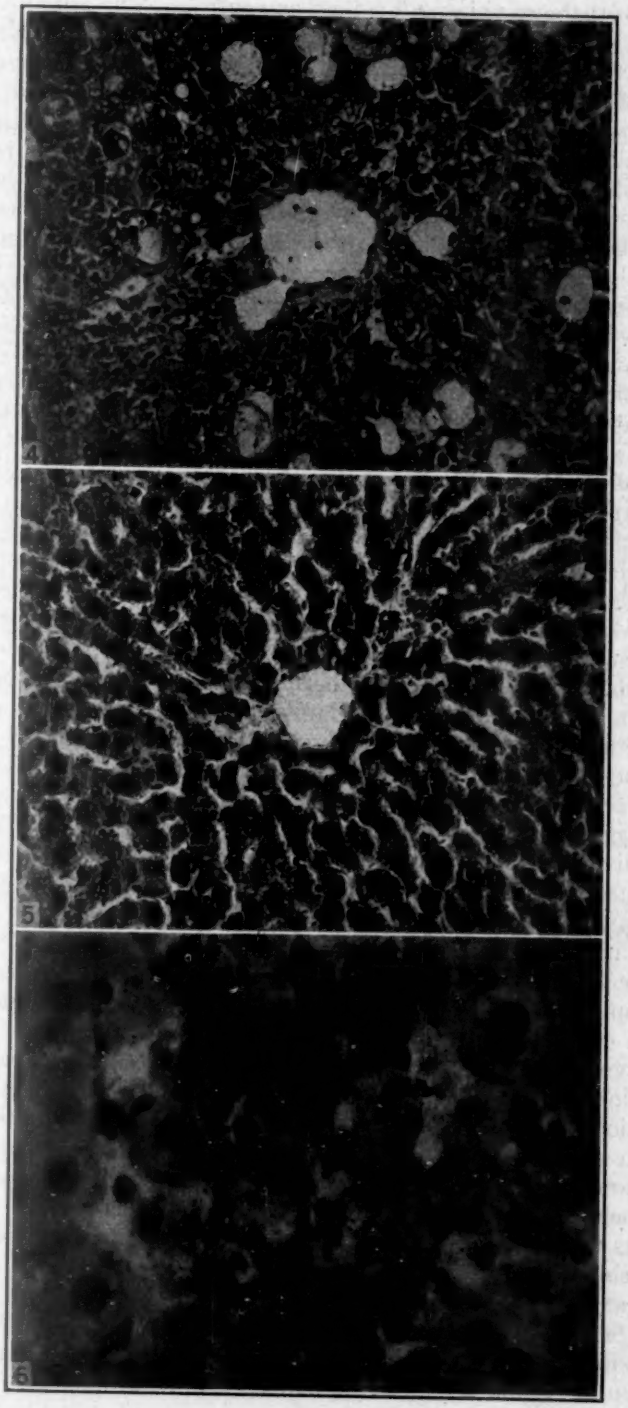
LEGENDS FOR PLATE ON OPPOSITE PAGE.

FIG. 4.—Liver of rat that received only inhalations of carbon tetrachloride daily for 2 weeks. There is a greater degree of central collapse and cellular infiltration than in the section in Figure 3, though the exposure to carbon tetrachloride was exactly similar in the 2 instances (H and E, × 200).

FIG. 5.—Liver of rat that received daily inhalations of carbon tetrachloride for 1 week and a daily administration of sulfanilamide for 2 weeks afterward. Complete restoration to normal was not impeded by the sulfanilamide (H and E, × 200).

FIG. 6.—Liver of rat that received alcohol daily for 4 weeks. Note the deposition of globules of fat in the cells from the periphery of the lobule. Stainable fat was not present in the sections of the livers of animals that received sulfanilamide also (Fat Stain: Sudan IV, × 560).



necropsy; the remaining 9 served as controls. The administration of the drug was begun on the day following operation. Necropsy was performed on 3 animals from each group at weekly intervals for 3 weeks and the livers were compared grossly and microscopically. Grossly, the livers of both groups were enlarged, firm and discolored with bile. In addition, the livers of the animals which had received sulfanilamide were black. The common and hepatic bile ducts were enormously distended in all cases. But microscopically no essential difference could be detected between these two groups of animals. There was no evidence of damage of the hepatic cells or of deposition of fat in any of the livers. Considerable proliferation of the bile ducts, most noticeable in animals living 3 weeks, was present to about the same degree in both groups.

Comment. The experiments cited here tend to indicate that the administration of sulfanilamide in moderately toxic doses does not increase the damage produced in the liver of a rat by carbon tetrachloride and that it does not impede regeneration of the liver after hepatitis has been induced by carbon tetrachloride. In fact, in the sections of the livers of the animals that had received both carbon tetrachloride and sulfanilamide, there was less damage than in those in which carbon tetrachloride had been administered alone. This observation is in accord with the recent report of Leach and Forbes that sulfonamide drugs act as protective agents against carbon tetrachloride poisoning. Furthermore, the simultaneous administration of alcohol with the sulfanilamide did not result in damage of the hepatic cells. Alcohol is regarded a substance which usually enhances the hepatotoxic effects of such drugs as phosphorus, chloroform or carbon tetrachloride. The drug likewise did not produce damage of the hepatic cells of animals that had obstructive jaundice. The livers of all animals that received sulfanilamide were dark brown or black as the result of contained blood discolored by the accumulation of various pigments responsible for cyanosis in animals or human beings receiving this drug.

These experimental data appear to be in accord with slowly accumulating clinical data which show that when sulfanilamide and allied compounds were administered to patients who had hepatic damage there were no apparent significant increases of hepatic dysfunction.[3,4,5,6,8,16,19] However, they do not shed any light on the question why, when patients receive sulfanilamide, hepatitis develops in some cases but not in others. A depression of hepatic function among patients receiving sulfanilamide has been reported.[18,21]

Conclusions. 1. The administration of sulfanilamide to a group of rats that were having hepatitis produced by inhalation of carbon tetrachloride did not increase the damage to the liver. On the contrary it appeared to lessen the damage.

2. Sulfanilamide after induction of hepatitis by means of carbon tetrachloride did not impede regeneration of the liver after administration of carbon tetrachloride had been discontinued.

3. The simultaneous administration of alcohol and sulfanilamide to rats did not result in damage of the hepatic cells, although in some of the animals that received only the alcohol, fat was deposited in the liver.

4. The administration of sulfanilamide to animals that had obstructive jaundice did not produce any detectable injury to the livers not ascribable to biliary obstruction.

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CHANGES IN COPPER AND IRON RETENTION IN CHRONIC DISEASES ACCOMPANIED BY SECONDARY ANEMIA.

II. Changes in Liver, Spleen and Stomach.

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In a previous study,[5] the retention of copper and iron in 146 patients with chronic diseases, predominantly malignancies, accom-

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panied by severe secondary anemia, was investigated. We found not only no shortage but actually a marked accumulation of these metals in the liver and spleen.

Gerlach[3] showed that the amount of copper in benign tumors was normal but varied in malignant growths. Edlbacher and Gerlach[1] found that in Jensen sarcoma the copper content differed according to the part of the tumor studied, necrotic tumor tissue containing more copper than the growing tumor. Sümegi[6] stated that in experimental rat cancer, copper was deposited in the liver and excluded from metabolism. He found 40% less copper than normal in the stomachs of his rats and interpreted this lack of copper as possibly responsible for inadequate formation of the anti-anemic factor.

Such a lack of copper in the stomach, if it were also present in human malignancies, might explain the accompanying anemia. We, therefore, studied stomach as well as liver and spleen tissue from malignant, non-malignant and normal cases.

Method. Copper was determined according to the method of McFarlane,[4] with slight modifications, iron according to the modified method of Elvehjem and Hart.[2] All values are expressed as milligrams in 100 gm. of dry tissue. Since material in Montefiore Hospital is derived from chronic cases, normal values for copper and iron in liver, spleen and stomach were established from tissue obtained in case of accidental death from the Medical Examiner's office at Bellevue Hospital.

TABLE 1.—IRON AND COPPER CONTENT OF LIVER, SPLEEN, STOMACH AND TUMOR TISSUE IN SECONDARY ANEMIA.

Figures Represent Mg. in 100 Gm. of Dry Tissue (Averages in Parenthesis).

Type of disease with number of cases examined.	Liver.		Spleen.	
	Iron.	Copper.	Iron.	Copper.
Normal controls (15)	17.2– 81.4 (44.7)	1.4–4.5 (2.8)	49.8–252.3 (137.2)	0.7–1.2 (0.9)
Malignancies (23)	12.5–1133 (124.2)	0.9–9.3 (3.8)	66.8–1776 (461.9)	0.8–3.6 (1.4)
Non-malignant cases (11)	29.0–247.0 (85.4)	1.5–7.2 (3.0)	61.9–721.8 (252.4)	0.8–2.7 (1.2)

Type of disease with number of cases examined.	Stomach.		Tumor tissue.	
	Iron.	Copper.	Iron.	Copper.
Normal controls (15)	16.3– 20.7 (18.2)	1.1–1.4 (1.3)		
Malignancies (23)	6.0– 79.9 (24.5)	1.1–2.2 (1.6)	17.7–130.1 (49.8)	1.2–4.2 (2.1)
Non-malignant cases (11)	19.3–137.8 (26.5)	0.8–2.3 (1.5)		

Findings. Iron in the spleen was greatly increased in about 50% of the malignancies, attaining levels in excess of 1000 mg. per 100 gm. of dry tissue, and up to 1776 mg. in a case of Hodgkin's disease. Copper storage in the spleen was either at the upper level of normal copper content, or exceeded it in 14 out of the 23 cases examined. Usually, greatly increased iron depots were paralleled by high copper

storage; there were instances, however, when iron was found to be normal in spite of a markedly increased copper content.

Iron in the liver was increased less frequently than in the spleen, only about one-third of the malignant cases showing high values. Copper storage was even less affected and exceeded the upper limit of normal in only 6 instances. But in these 6 a high copper level was not necessarily accompanied by a corresponding retention of iron. *Vice versa*, a level of 1133 mg. per 100 gm. of iron was associated with a normal copper value in a case of carcinoma of the ovaries.

Figures for iron in the stomach were at least normal in all and in excess of normal in 9 out of 16 cases. Usually, increased retention of iron was accompanied by increased retention of copper.

The striking affinity of tumor tissue for copper was demonstrated by values of 1.5 mg. per 100 gm. or more in 13 out of 18 tumors analyzed. Iron content ranged from 17.7 to 130.1 mg. per 100 gm., with the majority in the higher brackets. Material from a patient with Hodgkin's disease showed 1738 mg. of iron, but only 1.5 mg. of copper. This same case had 1776 mg. of iron in the spleen.

Iron and copper values in the non-malignant cases were in striking contrast to those encountered in malignancies. With few exceptions values for both elements were within normal in the spleen.

While levels of 479, 409.8 and 721.8 mg. per 100 gm. of iron were encountered in the spleen in instances of amyotrophic lateral sclerosis, arteriosclerosis and subacute bacterial endocarditis, respectively, they were exceptional. Similarly values of 1.4 and 2.7 mg. per 100 gm. of copper in the spleen in cases of coronary occlusion and essential hypertension respectively were also unusual. The liver showed a normal iron content in half and a normal copper content in all cases except in 1 of subacute bacterial endocarditis where 7.2 mg. were stored.

Iron in the stomach was elevated in all but 2 cases, though the only really high value was found in 1 of subacute bacterial endocarditis (137.8 mg.). Copper values were higher than normal in 6, normal in 4 and less than normal in 1 instance.

Discussion. It has been established that in severe secondary anemia there is not only no shortage, but actually a large accumulation of iron and copper in the liver and spleen. Extreme storage of these metals was found, especially in malignancies and marked retention in some non-malignant cases. Evidently a shortage of copper or iron or both could not be the prime factor responsible for anemia. Since a striking retention of iron and copper occurs in malignancies even without an accompanying anemia, anemia alone could not be responsible for the marked accumulation of these metals. Tumors and metastatic lesions showed marked accumulations of copper but these were not sufficiently large to explain the anemia.

Sümegi[6] found 40% less copper than normal in the stomachs of rats with experimental cancer. The question arose whether there was interference with formation of the anti-anemic factor due to an inadequate amount of iron or copper in the stomach. We found sufficient or excessive amounts of these metals in the stomach, in the majority of the malignancies. Similarly, in the non-malignant cases with severe anemia there was no shortage of iron or copper in the stomach and there was moderate retention. While Sümegi's work may offer an explanation for the anemia of rat cancer, it does not hold for anemia in humans whose stomachs show normal copper and iron values in anemia.

No correlation could be found between the impairment of nutrition and the degree of retention of copper and iron. Nor was there any rule which metal would be stored, or if both were retained, which would be retained more, though retention of iron was more common than that of copper.

It appeared that in spite of adequate amounts of iron and copper in the stomach, liver and spleen, the power to synthesize the blood-forming elements was impaired. Under such conditions, large amounts of iron and copper stored for emergency purposes cannot be utilized in the conversion of inorganic iron into hemoglobin. This view explains the apparent paradox of severe anemia despite excessive copper and iron storage in the depot organs.

The most interesting feature of this and the previous work was the finding of storage of iron and copper out of all proportion to the anemia in malignancies, which reached its highest degree in extensive metastatic disease. The few cases of malignancies without anemia with enormous amounts of copper and iron in the liver and spleen show that such accumulation can occur even in the absence of anemia, with malignancy as the only apparent causative factor. The factors responsible for the extremely high storage of iron and copper in the liver and spleen in malignancies could not be determined. Nevertheless, this finding was so striking and constant as to be significant.

Summary. 1. The content of iron and copper in liver, spleen, stomach and tumor tissue in chronic diseases accompanied by secondary anemia has been studied.

2. There is not only no shortage, but actually a large accumulation of iron and copper in liver and spleen in many cases of anemia. Extreme storage was found especially in malignancies, but was dependent on some factor other than the anemia.

3. Insufficient formation of the anti-anemic factor due to inadequate storage of iron or copper in the stomach suggested by Sümegi could not be the factor responsible for the anemia since at least normal, and in most cases higher than normal, amounts of these elements were present in the stomach.

4. Tumor tissue showed a high percentage of copper, indicating a

marked affinity for this element. This could not, however, have played a rôle in the production of anemia.

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PORTAL CIRRHOSIS.

A Correlation of Clinical, Laboratory, Peritoneoscopic and Autopsy Findings.

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During the past year, the opportunity has been presented for the study of 24 cases of hepatic disease that have proven to be portal cirrhosis of the liver in varying stages of development. Clinical and laboratory data together with peritoneoscopy and postmortem examinations were used in determining the diagnosis. An attempt to correlate the clinical and laboratory data has led to some observations which we consider of significance.

In the series of 24 cases, peritoneoscopic examination was performed in 20 cases, with postmortem examination being done on 3 of these cases. In 4 cases, postmortem examination alone was performed.

In order to simplify our results, we have adopted the classification of cirrhosis of the liver formulated by Connor[3] in a recent article. This classification appears to be in accord with most of the recent clinical and pathologic developments in the field of liver disease. He divides portal cirrhosis or chronic diffuse fibrosis of the liver into three main types.

1. Biliary cirrhosis, which is usually associated with biliary obstruction. The lesions begin in the portal areas around the bile ducts and the liver is usually large, tense, green and may be nodular.

2. Pigment cirrhosis, which is usually associated with the collection of irritating pigments and metals around the periphery of the

liver lobule. This is associated with periportal connective tissue proliferation. The liver is not usually decreased in size and has a smooth surface.

3. Fatty cirrhosis, in which the lesions develop around the lobule resulting from the fatty degeneration of cells around the periphery of the lobule, followed by fibroblastic proliferation. This type can be divided into three phases: (*a*) Acute fatty liver which occurs in the 40 to 45 age group. The liver is large, pale and greasy containing 60% fat and is usually smooth. This stage is also called fatty metamorphosis of the liver. (*b*) Fatty liver with early perilobular fibrosis which occurs in the 45 to 55 age group. The liver is large or normal and may be lobulated or smooth. This corresponds to hypertrophic fatty cirrhosis. (*c*) The atrophic phase or classical Laennec's cirrhosis in which the liver is smaller and grossly nodular and usually has a thickened capsule. This occurs in the 55 to 65 age group.

All of the 24 cases fall into the classification of portal cirrhosis. One case was the pigmentary type of cirrhosis, associated with sickle-cell anemia. Two of the cases fell into the classification of acute fatty liver or fatty metamorphosis. There were 16 cases of hypertrophic fatty cirrhosis and 5 cases of atrophic portal cirrhosis.

The diagnostic observations of the liver were performed by the peritoneoscopy service of Dr. LeRoy Sloan and Dr. Frank De Trana at the Cook County Hospital. The procedure of peritoneoscopy has been repopularized recently by Ruddock.[11] By this method direct endoscopic visualization of the liver is possible and in the hands of the trained observer, a definite diagnosis of the types of liver disease can usually be made, especially if it is the portal type of cirrhosis. This procedure is open to the criticism that biopsies are not made, although this can be done with the proper equipment, and that a histologic diagnosis is not obtained. However, peritoneoscopy is a relatively safe and convenient method for examining the peritoneal cavity and some of its contents, especially the liver. In cases of ascites or hepatomegaly of undetermined origin, it is often of great diagnostic aid.

A summary of the cases revealed that there were 19 men (16 white and 3 negro) and 5 women (3 white and 2 colored). The ages ranged from 17 to 75 years with 15 (62.5%) present in the fourth and fifth decades of life. Eighteen of the cases (75%) had a definite history of chronic alcoholism. Four cases had a history of syphilis, and of these, 2 had had indifferent treatment.

A review of the physical findings showed that all 24 cases had a usually well marked hepatomegaly and the liver extended 2 to 6 finger-breadths below the right costal margin. If the liver could not be palpated due to severe ascites, it could always be felt after paracentesis. The spleen was palpable in 6 of 24 cases (25%). Jaundice could be divided into three phases. Seven cases (29%)

had severe jaundice; 7 (29%) had moderate jaundice and 5 (20%) were subicteric. Upon correlating the type of liver disease with jaundice, it was found that in the one case of pigment cirrhosis associated with sickle-cell anemia, jaundice was the most prominent feature in the history, having been noted for 6 years before admission. In the 2 cases of acute fatty liver, or fatty metamorphosis, jaundice was marked on examination and prominent in the case history. In the 16 cases of hypertrophic fatty cirrhosis, jaundice was marked in both the history and physical examination in 7 of the cases, and was not prominent in the others. There were 5 cases of atrophic portal cirrhosis, in 3 of which jaundice was prominent in both the history and physical findings. Only 14 cases, (60%) exhibited marked ascites, and here the physical findings were misleading in that abdominal enlargement and other signs of fluid did not always indicate ascites when paracentesis was performed with the peritoneoscope. Pectoral alopecia was present in 6 of the 19 males (31%).

Thus the characteristic picture of the patient with portal cirrhosis was that of a male in the fourth and fifth decade of life, usually having a history of chronic alcoholism, always presenting a palpable liver and usually jaundice and ascites.

A summary of the laboratory data revealed some interesting findings. Examination of the blood revealed that 23 cases (96%) had some degree of anemia. In 16 cases (67%) an anemia characterized by macrocytosis or hyperchromia or both, was present. Six cases (25%) had some degree of secondary anemia, usually microcytic and hypochromic in nature. One case had a typical severe sickle-cell anemia and in one case no anemia was demonstrable.

The frequency of serum protein changes in parenchymal liver disease is well known, and this fact is borne out in our series of cases. The serum albumin fraction was less than normal in 23 of 24 cases (96%). The total serum protein was less than normal in only 3 of 24 cases (12½%). The serum globulin fraction was elevated in 21 of 24 cases (87%). If the normal albumin globulin ratio is considered to be 2:1, then the ratio was lowered in all 24 cases and totally reversed (*i. e.*, less than 1) in 16 of 24 cases (67%). Thus it can be seen that in this series of cases, the serum protein changes were profound.

The icteric indices of all 24 cases were above the normal level of 4 to 6, and varied from 9 to 150. Icteric indices above 10 were found in 21 of 24 cases. These findings appear to point out the frequency with which jaundice is associated with portal cirrhosis.

The hippuric acid test showed deficient liver function in 18 of 21 cases in which 2 was determined, (86%). There appeared to be a moderate correlation between the hippuric acid test and serum protein determinations as to the severity of liver damage. A bromsulphalein test was performed in one case and a glucose tolerance test in another, both showing evidence of decreased liver function.

TABLE 1.—SUMMARY OF DATA ON 24 CASES OF CIRRHOSIS.

Patient. Age. Sex. Color.	History and Physical examination.	Blood findings.	Total* serum protein.	Serum albumin.	Serum globulin.	Albumin globulin ratio.	Icteric index.	Liver function tests.	Pathologic diagnosis of liver (by peritoneoscopy unless otherwise stated).
1. F. G. 52 W M	Alcoholism 4+ Symptoms 2 yrs. incl. jaundice PX.—Jaundice 2 Pect. alopecia 0 Liver 5F down Ascites 4+ Spleen 0 Abd. veins 3+	Hgb 56% RBC 2,810,000 WBC 10,400 Anisocytosis Macrocytosis Hyperchromia	6.34	2.34	4.04	.58	51 44	Hippuric acid† 0.72 gm.	Enlarged, light gray, hobnailed. Hypertr. portal cirrhosis.
2. F. C. 42 C M	Lues. Moderate Rx Alcoholism 1+ Symptoms 2 mos. PX.—Subicteric Pect. alopecia 4+ Ascites 4+ Liver 5F down Spleen + Abd. veins 3+	Hgb 39% RBC 2,800,000 WBC 7200 Hypochromia Microcytosis Polychromatophilia	8.98	3.27	5.71	.57	17	Hippuric acid 3.34 gm.	Typical, hobnailed. Marked ascites. Hypertr. portal cirrhosis. Confirmed by autopsy 6 mos. later.
3. T. N. 54 W M	Alcoholism 0 Symptoms 2 mos. PX.—Subicteric Pect. alopecia 0 Ascites 4+ Liver 4F down Spleen 0 Abd. veins 2+	Hgb. 63% RBC 3,290,000 WBC 4000 Anisocytosis Macrocytosis	6.44	3.22	3.22	1.00	10	Hippuric acid 0.75 gm.	Enlarged, hobnailed. Marked ascites. Hypertr. portal cirrhosis.
4. C. Z. 50 W M	Alcoholism 4+ Symptoms 1 mo. incl. icterus PX—Jaundice 2+ Pect. alopecia 4+ Liver 6F down Ascites 3+ Spleen 0 Abd. veins 2+	Hgb 45% RBC 2,770,000 WBC 3650 Anisocytosis Macrocytosis	7.31	3.31	4.01	.80	50 51	Hippuric acid 2.37 gm.	Enlarged, dark yellowish-brown. Capsule is studded with translucent, pinhead-sized nodules. Fatty metamorphosis of liver. Tuberculous peritonitis.
5. W. P. 39 W	Alcoholism 4+ Symptoms 2 yrs. PX.—Jaundice 1+	Hgb 38% RBC 2,110,000 WBC 4900	7.03	2.46	4.57	.54	25	Hippuric acid 3.74 gm.	Enlarged, pinkish and finely nodular. No fluid present. Hypertr. portal cirrhosis.

	Liver 6F down Ascites 3+ Spleen 0 Abd. veins 3+	Macrocytosis							ules. Fatty metamorphosis of liver. Tuberculous peritonitis.
5. W. P. 39 W M	Alcoholism 4+ Symptoms 2 yrs. PX.—Jaundice 1+ Pect. alopecia 4+ Liver 3F down Ascites 2+ Spleen 0 Abd. veins 4+	Hgb 38% RBC 2,110,000 WBC 4900 Anisocytosis Hypochromia Poikilocytosis	7.03	2.46	4.57	.54	25	Hippuric acid 3.74 gm.	Enlarged, pinkish and finely nodular. No fluid present. Hypertr. portal cirrhosis.
6. J. S. 52 W M	Alcoholism 3+ Symptoms 2 mos. PX.—Subicteric Pect. alopecia 0 Liver 3F down Ascites 4+ Caput medusa Spleen 0	Hgb 55% RBC 2,590,000 WBC 11,200 Macrocytosis	5.54	2.34	3.19	.73	15	Hippuric acid 2.50 gm.	Coarsely granular. Mod. ascites. Hypertr. portal cirrhosis.
7. F. H. 28 C F	Alcoholism 0 Nine pregnancies Symptoms 4 mos. incl. jaundice PX.—Jaundice 2–3+ Liver 3F down Ascites 0 Spleen + Abd. veins 0	Hgb 45% RBC 3,040,000 WBC 7400 Diff. normal No sickling	6.12	2.81	3.31	.85	25 20	Hippuric acid 1.24 gm.	Enlarged, bright yellow smooth. Gall bladder and uterus normal. chr. left salpingo-oöphoritis. Fatty metamorphosis.
8. J. S. 45 W M	Alcoholism 4+ Symptoms 1 mo. PX.—Jaundice 0 Pect. alopecia 0 Liver 5F down Ascites 0 Spleen 0 Abd. veins 1+ Old appendect. scar	Hgb 59% RBC 2,840,000 WBC 4400 Diff. normal	5.72	3.41	2.31	1.80	9	Hippuric acid 3.57 gm.	10 cm. below costal margin; is light gray and finely granular. Gall bladder light gray and thickened. Many adhes. bet. rt. lobe, liver and diaphragm. Hypertr. portal cirrhosis. Old healed peritonitis.

TABLE 1.—(*Continued*)

Patient. Age. Sex. Color.	History and Physical examination.	Blood findings.	Total* serum protein.	Serum albumin.	Serum globulin.	Albumin globulin ratio.	Icteric index.	Liver function tests.	Pathologic diagnosis of liver (by peritoneoscopy unless otherwise stated).
9. C. C. 52 W M	Alcoholism 4+ Symptoms 6 wks. incl. jaundice PX.—Jaundice 4+ Pect. alopecia + Liver 5F down Ascites 4+ Spleen 0 Abd. veins 3+	Hgb 23% RBC 2,750,000 WBC 14,200 Anisocytosis Macrocytosis	7.65	2.65	5.00	.53	100 150	Hippuric acid 0 gm.	Enlarged, surface finely granular. Marked ascites. Hypertr. portal cirrhosis.
10. D. O. 48 W M	Alcoholism 4+ Lues with no Rx Symptoms 2 yrs. incl. jaundice PX.—Jaundice 3+ Pect. alopecia Liver 4F down Ascites 0 Spleen 0 Abd. veins 0	Hgb 73% RBC 3,500,000 WBC 8200 Diff. normal	5.66	2.81	2.85	.99	75	Hippuric acid 1.41 gm. Wass. and Kahn negative	Enlarged, dark gray green and hobnailed. Also simple cyst, rt. lobe. Hypertr. portal cirrhosis.
11. W. W. 48 W M	Alcoholism 4+ Lues with moderate Rx Symptoms 1 yr. incl. jaundice PX.—Jaundice 3+ Pect. alopecia + Liver 4F down Ascites 0 Spleen 0 Abd. veins 0	Hgb 69% RBC 3,500,000 WBC 8200 Diff. normal	8.34	3.12	5.22	.59	60	Hippuric acid 2.21 gm. Kahn neg.	Enlarged and hobnailed. Gall bladder distended, and wall thickened. Hypertr. portal cirrhosis. Chr. cholecystitis.
12. D. P. 52 C F	Alcoholism 4+ Symptoms 1 mo. incl. jaundice PX.—Jaundice 3+ Liver 3F down Ascites 4+ Spleen 0 Abd. veins 3+	Hgb 84% RBC 5,100,000 WBC 5900 Diff. normal	7.81	3.75	4.06	.92	75	Hippuric acid 1.56 gm.	Coarsely hobnailed. Gall bladder normal. Marked ascites. Exploratory laparotomy, Talma oper. and biopsy revealed portal cirrhosis. Autopsy 1 mo. later, atrop. portal cirrhosis.
[illegible] 52 W M	[illegible] Symptoms 1 mo. PX.—Subicteric Pect. alopecia 0 [illegible]	[illegible] RBC 4,580,000 WBC 10,000 Anisocytosis Macrocytosis	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible] 2.89 gm. Glucose toler. test, normal curve	[illegible] lar. No fluid present. Early hypertr. portal cirrhosis.

	Ascites 4+ Spleen 0 Abd. veins 3+									ma oper. and biopsy revealed portal cirrhosis. Autopsy 1 mo. later, atrop. portal cirrhosis.
13. J. C. 52 W M	Alcoholism 3+ Symptoms 1 mo. PX.—Subicteric Pect. alopecia 0 Liver 3F down Ascites 0 Spleen 0 Abd. veins 0	RBC 4,580,000 WBC 10,000 Anisocytosis Macrocytosis Hyperchromia						2.89 gm. Glucose toler. test, normal curve	lar. No fluid present. Early hypertr. portal cirrhosis.
14. C. Y. 56 W M	Alcoholism 2+ Symptoms 2 wks. PX.—Subicteric Pect. alopecia 0 Liver 4F down Ascites 0 Spleen 0 Abd. veins 0	Hgb 60% RBC 2,660,000 WBC 13,200 Anisocytosis Macrocytosis Hyperchromia	5.85	3.75	2.10	1.78	18.7	Glucose toler. test shows hyperglycemic curve Bl. cholest. 208 Bl. cholest. esters 59	Enlarged, finely granular. No ascites. Hypertr. portal cirrhosis.
15. W. G. 72 C M	Alcoholism 3+ Lues denied Symptoms 1 mo. PX.—Subicteric Pect. alopecia Liver 2F down Ascites 4+ Spleen 0 Abd. veins 3+	Hgb 75% RBC 3,800,000 WBC 5450 Anisocytosis Macrocytosis	8.65	2.34	5.31	.44	18.7	Hippuric acid 1.53 gm. Kahn 2+ Wass. 4+	Smaller than normal; diffuse hobnail. Marked ascites. Atrophic portal cirrhosis.
16. J. D. 62 W M	Alcoholism 3+ Symptoms 1 mo. incl. jaundice PX.—Jaundice 2+ Pect. alopecia 0 Liver 4F down Ascites 2+ Spleen 0 Abd. veins 1+	Hgb 80% RBC 4,130,000 WBC 12,500 Anisocytosis Macrocytosis	7.81	3.85	3.96	.97	50	Hippuric acid 1.06 gm.	Enlarged, has typical granular appearance. Sl. ascites. Hypertr. portal cirrhosis.
17. I. S. 50 W F	Alcoholism 2+ Symptoms 1 mo. incl. jaundice PX.—Jaundice 2+ Liver 4F down Ascites 2+ Spleen 0 Abd. veins 3+	Hgb 44% RBC 1,910,000 WBC 8250 Macrocytosis	7.99	2.56	5.43	.49	30	Hippuric acid 1.01 gm.	Enlarged and finely hobnailed. Hypertr. portal cirrhosis.

TABLE 1.—(*Continued*)

Patient. Age. Sex. Color.	History and Physical examination.	Blood findings.	Total* serum protein.	Serum albumin.	Serum globulin.	Albumin globulin ratio.	Icteric index.	Liver function tests.	Pathologic diagnosis of liver (by peritoneoscopy unless otherwise stated).
18. D. H. 71 W F	Alcoholism 1+ Yellow fever in childhood, symptoms 2 mos. PX.—Jaundice 0 Liver 4F down Ascites 4+ Spleen 0 Abd. veins 3+	Hgb 41% RBC 2,830,000 WBC 4600 Anisocytosis Macrocytosis Hyperchromia	5.10	3.16	1.94	1.62	16	Hippuric acid 1.94 gm.	Enlarged; capsule thickened; surface coarsely granular. Uterus and tubes normal. Hypertr. portal cirrhosis.
19. L. H. 58 C F	Alcoholism 0 Symptoms 2 wks. PX.—Jaundice 0 Liver 3F down Ascites 3+ Spleen 0 Abd. veins 2+	Hgb 38% RBC 3,130,000 WBC 6500 Anisocytosis Microcytosis Hypochromia	7.50	4.37	3.13	1.40	18	Hippuric acid 2.48 gm.	Enlarged, grayish-brown and surface irregularly granular. Gall bladder shows many adhesions to adj. liver. Pelvis normal. Hypertr. portal cirrhosis. Chr. cholecystitis.
20. J. D. 36 W M	Alcoholism 4+ Symptoms 2 mos. incl. jaundice PX.—Jaundice 4+ Pect. alopecia 0 Liver 3F down Ascites 4+ Spleen + Abd. veins 1+	Hgb 68% RBC 3,520,000 WBC 7500 Anisocytosis	6.51	2.96	3.55	.83	100	Hippuric acid trace Bl. cholest. 128 Bl. cholest. esters, 21	Autopsy revealed hyper. portal cirrhosis with marked icterus and icteric nephrosis.
21. E. S. 49 W M	Alcoholism 4+ Lues—moderate Rx Symptoms 2 wks. PX.—Subicteric Pect. alopecia 0 Liver 5F down Ascites 2+ Spleen + Abd. veins 3+	Hgb 63% RBC 3,080,000 WBC 7150 Anisocytosis Macrocytosis	6.38	3.20	3.18	1.05	25	Hippuric acid 1.23 gm. Wass. negative	Enlarged and coarsely granular. Hypertr. portal cirrhosis.
22. C. N. 75 W M	Alcoholism 4+ Symptoms 2 yrs. PX.—Subicteric Pect. alopecia 0	Hgb 51% RBC 3,690,000 WBC 10,750 Hyperchromia	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible] test, 75% retention	portal cirrhosis and adenocarc. of cecum with metastases to the liver.

	Pect. alopecia 0 Liver 5F down Ascites 2+ Spleen + Abd. veins 3+	Macrocytosis							
22. C. N. 75 W M	Alcoholism 4+ Symptoms 2 yrs. PX.—Subicteric Pect. alopecia 0 Liver 3F down Ascites 4+ Spleen 0 Abd. veins 0	Hgb 51% RBC 3,690,000 WBC 10,750 Hyperchromia Anisocytosis Poikilocytosis	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible] test, 75% retention	[illegible] portal cirrhosis and adenocarc. of cecum with metastases to the liver.
23. E. W. 17 C M	Alcoholism 0 Jaundice for sev. yrs., abd. enlargement PX.—Jaundice 4+ Pect. alopecia Liver 6F down Ascites 0 Spleen 0 Abd. veins 0	Hgb 27% RBC 1,500,000 WBC 25,000 Anisocytosis Poikilocytosis 75% sickling of red blood cells	7.50	3.48	4.02	.85	150	Bl. cholest. 101 Wass. negative	Autopsy: Marked jaundice and periportal (hypertrophic) type of cirrhosis of pigmentary etiology.
24. D. W. 64 W M	Alcoholism 0 Symptoms 3 mos. incl. jaundice PX.—Jaundice 2+ Pect. alopecia 0 Liver 2F down Ascites 1+ Spleen 2+ Abd. veins 1+	Hgb 43% RBC 2,105,000 WBC 3700 Hyperchromia Anisocytosis Poikilocytosis	7.19	3.80	3.39	1.12	37.5	Hippuric acid 2.71 gm.	Autopsy: Atrophic fatty portal cirrhosis of liver. Jaundice.

* The serum proteins were determined by the modified method of Kraus (J. Lab. and Clin. Med., **25**, 1300, 1940).

† The hippuric acid determinations were estimated by a modified method of Kraus and Dulkin (J. Lab. and Clin. Med., **26**, 729, 1941). Normal excretion of hippuric acid in 4 hours when 5.9 gm. of sodium benzoate are fed is estimated as from 3 to 5 gm.

Unless otherwise indicated, the blood serological tests were negative.

Thus, 20 of 23 cases (83%) showed decrease in liver function as determined by the hippuric acid, bromsulphalein and glucose tolerance test, whereas the serum protein tests showed liver damage in all cases.

Discussion. The correlation of data collected in this study has brought up some points that we wish to stress.

First, the correlation between alcoholism and cirrhosis in man is noted in our cases, as it has been elsewhere. However, it is well to remember that, as yet, no one has produced portal cirrhosis experimentally by the use of alcohol. In a recent article, Mallory[9] discussed various toxic substances which are known to cause parenchymal liver disease such as halogenated hydrocarbons, arsphenamine, selenium, and so on, and states that alcohol cannot yet be called the cause of portal cirrhosis.

The association of jaundice with portal cirrhosis, we feel, has not received sufficient consideration. It has been our impression that students have been taught that jaundice is not frequently associated with portal cirrhosis of the liver, and that when it does occur, it is a late or terminal manifestation. Richard Cabot classifies jaundice in his book "Differential Diagnosis." Excluding icterus neonatorum and sepsis of 661 cases of jaundice, only in 48 (7.1%) was the cause considered to be portal cirrhosis, which would tend to substantiate the above belief. In Tice's "Practice of Medicine," the section on diseases of the liver by Elliot and Nadler states that jaundice is not a prominent feature of portal cirrhosis, but that it is encountered at some stage in over one-third of the cases. Samuel Weiss in his book, "Diseases of the Liver, Gall Bladder, Ducts and Pancreas," states that early in the course of portal cirrhosis jaundice is not usually present. Later, when hepatic insufficiency is pronounced, there is said to be a subicteric tint to the skin, or the patient may be jaundiced, and also if jaundice occurs at all, it is of the catarrhal type and considered a complication.

Foley, Keeton, Kendrick and Darling[55] reported 21 cases of liver disease and an analysis of their cases revealed that 20 out of 21 had higher icteric indices than normal. All of the cases were portal cirrhosis, except one of acute yellow atrophy. However, this finding was not stressed in their paper.

We have noted the frequency of jaundice in our series of cases. It did not appear to be related to the duration of the disease, and in fact occurred in the early stages of portal cirrhosis (*i. e.*, the acute fatty liver and the hypertrophic fatty stage) as frequently as in the later stages. The history of the onset of jaundice is often difficult to obtain, but it is frequently one of the earliest and most prominent symptoms in the case history. This high incidence of jaundice would lead us to the impression that liver damage of sufficient nature to cause a regurgitant or toxic type of jaundice may occur relatively early in the course of portal cirrhosis. This can be noted in the

correlation of the presence of jaundice with the various phases of portal cirrhosis. From the viewpoint of pathogenesis, it is believed that actual damage to the liver cells is the first step in the development of portal cirrhosis. Fibrosis and regeneration of the liver cells occurs later and it is reasonable to assume that decrease of liver function and jaundice, which is an expression of this, can occur early in portal cirrhosis, and may be progressive or intermittent, depending on the regenerative ability of the liver. The progression of the earlier forms of liver damage, such as the so-called catarrhal jaundice, simple jaundice, and so on. to the chronic stages of liver disease, has been observed clinically by Bloomfield[2] and other observers. He has been able to demonstrate that portal cirrhosis may begin as a catarrhal jaundice, and that acute exacerbations of "hepatitis," characterized by jaundice, can occur during the course of the disease. This fits in with the experimental observations on cirrhosis and tends to confirm our impression of the presence of jaundice during the course of this disease.

We have noted that 96% of this series of cases exhibited some degree of anemia, 67% of which was macrocytic or hyperchromic in type. However, this association of marked anemia with cirrhosis and other chronic liver disease has not been greatly emphasized until very recently. Wintrobe,[14] however, found that in 44 cases of cirrhosis, 41% had a macrocytic anemia, 34% had a normocytic anemia and 9% had a hypochromic anemia. This anemia was attributed to the failure of storage of extrinsic factor in the liver, due to the pathologic changes present. Bianco and Jolliffe,[1] in a study of the anemia of the alcohol addict, observed that in 30 patients with alcoholic cirrhosis, 70% were anemic, and in 53% this anemia was macrocytic in type and associated with hyperchromia. They attributed the anemia to extrinsic deficiency of some necessary hematopoietic substance required to maintain normocytosis.

The alteration of serum proteins in diseases of the liver, particularly portal cirrhosis, has been well-known since the work of Grenet[7] and Gilbert and Cheray.[6] Numerous investigators have reported the lowering of total serum protein, especially of the albumin fraction, and the lowering or reversal of the albumin globulin ratio. Meyers and Keefer[10] and Foley, *et al.*,[5a] have reported such changes as occurring in all of their cases of portal cirrhosis, and also other types of chronic liver disease. Tumen and Bockus[13] reported 45 cases of acute and chronic liver disease in which hypoalbuminemia was the most constant feature noted, being present at some time in practically every case of chronic advanced liver disease and in most cases of obstructive jaundice. They found an elevation of the serum globulin and a lowering of the albumin globulin ratio usually present but did not think this as significant as a lowering of the serum albumin.

Our results coincide with previous findings as regards the lowering

of serum protein, especially the albumin fraction and a rise of the globulin fraction, with reversal of the albumin globulin ratio. The serum protein determinations appear to be the most constant and perhaps earliest means of determining the severity of liver damage, as borne out by the results in comparison with other liver function tests.

In this connection it is interesting to note the work of Kirshbaum and Popper,[8] in a series of cases of toxic hepatitis of a form intermediate between so-called catarrhal jaundice and acute yellow atrophy. They found changes consisting of enlargement of the liver and characterized histologically by damage to the liver cells and a serous hepatitis with dissociation of the liver cord cells. Edema of the liver was marked due to the fact that the Disse spaces, between the blood capillaries and the liver cord cells, were markedly widened and contained coagulated proteins. The presence of these proteins led to the assumption that there was capillary damage with exudation of serum protein, and the damage was assumed to be due to the toxic agent present. When the amount of escaped protein was high, there was an increasing accumulation of fluid between the cords of liver cells, due to the decrease of the colloid osmotic pressure of the blood. This fluid pressure finally destroyed the structure of the liver cells, giving the picture of severe dissociation. This was synonymous with "serous hepatitis" which occurs in the severest form in the liver of beriberi. This may be a possible explanation for the serum protein changes in parenchymatous liver disease, for here is an actual loss of blood protein from the circulation. Since the liver is tied up with the intermediary metabolism of serum protein, especially albumin, the actual liver damage would prevent or inhibit the reformation of the lost protein.

In a series of dogs, Elman and Heifetz[4] produced a 50% fall in the albumin fraction of the plasma by dietary means, without a change in the globulin. As the hypoalbuminemia progressed there were severe changes in the liver, consisting of increase of the water content and a fall in the protein content and vacuolation of the liver cells. There was definite impairment of liver function. Thus we have corollary evidence of the effect of protein deficiency on the liver and on the serum protein levels.

It would seem plausible then to state that there are two factors concerned in the pathogenesis of portal cirrhosis. One is the dietary deficiency of protein, which appears to be prominent in the cirrhotic as evidenced by fall in serum protein, especially of albumin and the change in the albumin globulin ratio. The presence of macrocytic anemia, neurologic manifestations and often frank pellagra in the cirrhotic also points to this, as has been emphasized by Snell.[12] The prominence of alcoholism in the case history is explained by the fact that many alcoholics subsist on very little food during their debauches. Also, cirrhosis of the liver is endemic in regions where widespread nutritional deficiencies are common, as in

China. The work of Elman and Heifetz is corollary evidence that nutritional deficiency of protein alone can cause liver damage.

We have reviewed pathologic evidence that certain toxins can affect the liver by causing capillary damage and exudation of serum protein. It would seem logical to assume that a combination of the two factors of protein deficiency and toxic capillary damage in the liver could explain the pathologic picture of early liver damage and that a progression of these changes would eventually lead to a classical portal cirrhosis.

Summary. A series of 24 cases of portal cirrhosis of the liver in varying stages was studied in an attempt to correlate clinical and laboratory findings. The diagnosis was confirmed by peritoneoscopy in 20 cases and by postmortem examination in 4 cases. Marked change in the serum albumin and globulin were noted in 100% of the cases. There was a marked tendency to the lowering of the serum albumin and a rise of the serum globulin with a consequent lowering of the albumin globulin ratio in all cases. There was a reversal of the albumin globulin ratio in two-thirds of the cases. Jaundice was a fairly constant feature being present in some degree, as measured by the icteric index in all cases. Jaundice was evident on physical examination in 79% of the cases. Changes in the peripheral blood were marked in 96% of the cases. A macrocytic or hyperchromic anemia was present in 67% of the cases while 25% exhibited a microcytic or hypochromic anemia. One case presented a typical severe sickle-cell anemia. Deficiency of liver function, as determined mainly by the hippuric acid test and also by a glucose tolerance and a bromsulphalein test, was noted in 83% of the cases. When the serum protein determinations were utilized as a liver function test, 100% of the cases exhibited a diminution of liver function.

A correlation of clinical and laboratory findings together with peritoneoscopic examination of the liver and postmortem analysis would appear to offer useful fields of investigation in liver disease.

A possible explanation of some etiologic factors in portal cirrhosis damage to liver cells, toxic hepatitis, catarrhal jaundice, acute yellow atrophy is offered.

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TREATMENT, COMPLICATIONS AND DEATHS IN 753 CASES OF CLINICAL DIPHTHERIA.

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Between July 1, 1937, and June 30, 1940, there were 753 cases of diphtheria admitted to the Los Angeles County General Hospital, of whom 48% were males and 52% were females. The admissions have followed a consistent downward trend each year since 1932, though the comparative yearly mortality for the period studied showed no appreciable difference (5% for the first 2 years as compared to 4.2% for the last year). This decline in incidence may well be due to natural trends as well as to an extensive immunization program.

Age Distribution with Deaths and Fatality Rate. Table 1 shows the age distribution of cases, the number of deaths in each group, and the fatality rate. Note that the incidence of diphtheria under one year of age was extremely low. The majority of cases (61%) occurred before the age of 10, the subsequent incidence gradually diminishing to the age of 65. This is similar to the published reports of Gordon[6] in Detroit and of Hoyne[7] in Chicago. The case fatality rate showed no marked difference for the small number of cases. The infant fatality rate was 41.6%. There were only 2 deaths after the age of 15; one was a male age 37, a chronic alcoholic ill for 7 days before admission, and the other a male age 47 ill 8 days before admission and who died within 4 hours after admission.

Duration of Illness Before Administration of Antitoxin. Of our patients 60% were admitted on or before the third day of their illness and the average time before the administration of antitoxin in 713 cases was 3.7 days. In 40 cases the duration was unknown. Among the fatal cases the average time was 5 days, which bears out the frequently observed fact of increasing risk after the third day of illness.

TABLE 1.—DISTRIBUTION OF CASES AND DEATHS ACCORDING TO AGE GROUPS.

Age.	Cases.	Deaths.	Case fatality rate %.
0– 1	12	5	41.6
1– 5	229	18	7.8
5–10	218	9	4.1
10–15	80	2	2.5
15–20	52	0	0
20–25	43	0	0
25–30	50	0	0
30–35	19	0	0
35–40	22	1	4.5
40–45	10	0	0
45–50	9	1	11.1
50–55	4	0	0
55–60	2	0	0
60–65	3	0	0
Total	753	36	4.8

Distribution of Lesions. Of our cases 53% were simple tonsillar diphtheria. There were no deaths in this group and none in the few cases of nasal pharyngeal or pharyngeal diphtheria. One case of diphtheria limited to the eye and one case in a burn associated with scarlet fever were noted: the former required enucleation and the latter skin grafts; both recovered. Table 2 shows the distribution of cases with location of the membrane, the presence of the "bull neck" type of infection, and the mortality in the separate groups. The fatality rate is high in the group so aptly described as "bull neck." In these patients the tissues of the neck externally and internally show marked edema and induration as well as lymphadenopathy. The membrane tends to spread rapidly and assume a dirty, necrotic appearance, and often the involvement is so extensive that the airway is obstructed through the nostrils and pharynx. In such cases increased pulse rate associated with increased respiration and temperature are regarded as indications for tracheotomy even without suprasternal retractions or cyanosis. Experience teaches that intubation is unwise in these cases. There was a mortality of 100% in 9 cases of the "bull neck" type in which the membrane extended into the larynx, trachea, and bronchi.

Dosage of Antitoxin. The dosage of antitoxin was determined by the apparent toxemia, the extent of the membrane, and the duration of the illness; neither weight nor age was used as a criterion. Twenty-eight per cent each of the total of 753 patients received 20,000, 30,000, and 40,000 units respectively; less than 4% received less than 20,000 units, and 12% received varying amounts over 40,000 units. Laryngeal cases were never given less than 40,000 units. Two patients did not receive antitoxin; one of these was moribund and died within an hour, and the other had almost recovered when admitted to the hospital.

General Therapy. Therapy in the early stages of diphtheria consists in adequate doses of antitoxin, *complete* bed rest, constant

nursing care, an adequate dietary and vitamin regimen, and intravenous dextrose and insulin. The diagnosis is determined as rapidly as possible and treatment is begun in the admitting ward. If the skin test for serum sensitivity is negative, intramuscular antitoxin is given ½ hour later; severely toxic patients may receive intravenous antitoxin diluted in 200 cc. to 400 cc. of physiologic saline. Dextrose

TABLE 2.—DISTRIBUTION OF MEMBRANE AMONG CASES WITH MORTALITY OF EACH VARIETY.

Type.	Bull neck. Cases.	Bull neck. Deaths.	Bull neck. Case fatality, rate %.	Total. Cases.	Total. Deaths.	Total. Case fatality, rate %.
Nasal	0	0	0.0	48	1	2.1
Nasal Pharyngeal	0	0	0.0	13	0	0.0
Nasal Tonsillar Pharyngeal	9	5	55.5	48	6	12.5
Tonsillar	11	0	0.0	401	0	0.0
Tonsillar Pharyngeal	25	7	28.0	111	7	6.3
Pharyngeal	0	0	0.0	8	0	0.0
Tonsillar Pharyngeal Laryngeal	1	1	100.0	59	6	10.2
Nasal Tonsillar Pharyngeal Laryngeal	3	3	100.0	19	4	21.1
Nasal Tonsillar Pharyngeal Laryngeal Tracheo Bronchial	5	5	100.0	8	8	100.0
Laryngeal	0	0	0.0	36	4	11.1
Comp. wound Scarlet	0	0	0.0	1	0	0.0
Eye	0	0	0.0	1	0	0.0
Total	54	21	38.8	753	36	4.8

solution is never used; it precipitates the antitoxin. All patients are placed at absolute flat bed rest, and, where necessary, in Trendelenburg position for postural drainage. Patients placed with their heads down must be watched with extreme care, as plugs may form in the bronchi. In some instances such plugs have required bronchoscopic removal to save life. Ordinarily, after a short period of drainage it is better to keep the patient flat, and in some instances it has proved beneficial to instill a drop or two of normal sterile saline through the tube at short intervals in tracheotomized cases. Since instituting this method, we have had remarkable freedom from the drying out effect and complicating mucous plugs resulting therefrom. Fluids are forced, especially in the form of dextrose; if necessary, this is given intravenously. Vitamin B complex and vitamin C are given in large doses. Barbiturates and bromides are used to alleviate restlessness; opiates are avoided.

Complications. *Myocarditis.* Circulatory failure associated with toxic myocarditis is an important problem because of the large number of deaths chargeable to it. The prophylactic value of prompt recognition of this condition followed by immediate and adequate therapy cannot be overstressed. In pharyngeal and nasopharyngeal diphtheria the absorption of toxin is rapid because of the large vascular bed at the site of the membrane. Nevertheless, if adequate doses of antitoxin are given early the fatality rate is low; otherwise it increases rapidly unless other measures are used.

Most workers classify circulatory failure into two groups, early and late. Early circulatory failure is an essential part of the diphtheritic toxemia while late circulatory failure is a complication occurring during convalescence, in the stage of local inflammatory reaction of regeneration and repair.[4,6,8,9,11]

During recent years,[2] following the work of Hoyne[7] and Gordon[6] we have been able to prevent and to reduce the mortality of diphtheritic myocarditis. Prophylactically, dextrose is administered intravenously without waiting for physical signs to appear; insulin is also administered to prevent the excessive spill-over and to facilitate the assimilation of dextrose. In 1927 Gordon first used dextrose routinely in early toxic diphtheria and was followed by Toomey[10] in 1928. Early in 1934 Hoyne gave it routinely to all patients in the following groups: "1, those ill more than 3 days prior to receiving antitoxin; 2, 'bull neck' type regardless of which day the antitoxin had been injected; 3, patients with marked albuminuria; 4, all postnasal cases and all malignant types of any character." His fatality rate was reduced to 9.8% from the usual 30 to 60%.

Treatment in late circulatory failure differs from that of early circulatory failure because the mechanism of failure is different. In addition to the myocarditis, involvement of the peripheral vasomotor mechanism has been demonstrated. In solving this problem the rationale of Dr. Gordon has been followed. The pressor principle of pituitary extract is used to restore and maintain blood pressure adequate for efficient circulatory function. It is imperative that the patient be well hydrated before the pitressin is given to avoid the undesirable reactions of shock, emesis, pallor and blanching of the skin. One-fourth to 1 cc. of pitressin is given subcutaneously every 8 hours, or oftener if indicated. Blood pressure readings are taken every 5 to 15 minutes until the blood pressure has returned to normal limits for the individual. Treatment must be continued until such normal blood pressure is reached, which may take a period of days and demands a knowledge of the normal blood pressure of small children. At variable intervals after pitressin has been given a compensatory diuresis occurs. It then becomes necessary to rehydrate the patient and repeat the pitressin. Each case must be strictly individualized and never become routine in its handling. Recently we have also used adrenal cortex (eschatin) in doses of

10 to 20 cc. to maintain blood pressure. Drugs such as caffeine-sodium-benzoate and adrenalin are not effective.[3] Digitalis is contraindicated and its use is strongly condemned; it increases toxicity rapidly.[5]

During the year 1937 electrocardiograms were taken on all cases of diphtheria whenever possible. This was usually done between the tenth and fourteenth days of the disease. During 1938–1940 electrocardiograms were taken only in those cases showing pulse irregularity or clinical evidence of myocarditis. In this series there were 278 cases in which electrocardiograms were taken. Changes giving evidence of myocardial damage were found in 29 cases (10%). The abnormalities and lesions are tabulated in Table 3. Fifty per cent of the total deaths showed evidence of myocarditis clinically or at autopsy. In this group of 18 deaths bronchopneumonia occurred 11 times, "bull neck" 12 times, and tracheotomy had been needed 11 times.

TABLE 3.—VARIATIONS IN ELECTROCARDIOGRAPHIC RECORDINGS IN 279 CASES OF CLINICAL DIPHTHERIA.

	No. of cases.
Myocardial damage	29
Rhythm:	
Nodal	2
S–A	118
S–T	103
Aur. extrasystoles	1
Vent. extrasystoles	2
Shifting pacemaker	1
Axis deviation:	
Left	37
R+	55
None	187
Incr. pr. interval	3
Incr. intravent. cond.	4
Slurring QRS (2 or more)	29
Low voltage QRS (2 or more)	44
T wave changes:	
Flat T_1	10
Flat T_2	9
Inverted T_1	4
Inverted T_2	4
Diphasic T_1	0
Diphasic T_2	2
S–T interval deviations	8
Total	279

A case history is offered as an example of therapy just discussed in a patient showing evidence of marked toxemia, myocardial damage as demonstrated by electrocardiograms, and marked peripheral vasomotor collapse. Cases showing bundle branch block are fatal in a large percentage of those reported.

Case History. C. E. W., female, Caucasian, age 6 years, onset of illness was 2 days before admission, December 10, with fever, sore throat, and

dysphagia. A positive throat culture for diphtheria was obtained the day before admission. The patient was a well-developed and well-nourished child, flushed, toxic, acutely ill. Temperature was 101.4°, pulse 140, and respirations 24. There was a tender, non-fluctuating indurated swelling, lemon-size, extending from the left submaxillary region to the mastoid. The throat showed marked edema and swelling particularly on the left, the uvula being pushed to the right. Membrane covered this area and extended to the soft palate and right tonsil. The pharynx was obstructed by swelling and mucus. No respiratory distress was apparent. The lungs were clear, the heart normal, and the remainder of the examination negative.

The laboratory reported positive smears and cultures for Klebs-Loeffler bacilli. The blood count was not remarkable, and the urine normal except for albumin present on three occasions. A Roentgen Ray examination on January 16 showed the heart within normal limits, and no evidence of parenchymal infiltration.

Following negative skin tests, 10,000 units of diphtheria antitoxin were given intravenously and 30,000 units intramuscularly. During the first 2 weeks in the hospital the patient received daily 1000 cc. of 5% glucose intravenously covered by adequate insulin. On December 15 and 16 a slight drop in blood pressure was noted (82/53). The heart tones, however, were regular and of good quality. On December 17 there was a rapid progressive drop in blood pressure (50/?), marked pallor of the face, abdominal pain, weak pulse, and general evidence of circulatory collapse. Eschatin, pitressin, and 10% glucose intravenously were given with gradual improvement during the following 2 or 3 days.

Serial electrocardiograms were taken as illustrated in Figures 1 and 2. These electrocardiograms were chosen from the series as demonstrating significant serial changes. Clinically, occasional dropped beats, extrasystoles, and a soft apical murmur were noted. The patient was discharged on March 11 as cured, and advised to continue with moderate rest.

Bronchopneumonia. Bronchopneumonia was reported in 80 cases. Terminally, it was present in 12 postmortem examinations and reported clinically in 8 other deaths. In recent years it has responded readily to the sulfonamide drugs.

Asphyxia and Stenosis. Infection limited to the larynx and below it becomes primarily a problem of asphyxia from mechanical obstruction rather than toxemia. The use of the bronchoscope and aspiration of the membrane through it or through the tracheotomy tube was instituted under the supervision of our consultant, Dr. Alden Miller. This procedure has reduced the fatality rate from asphyxia to 11% of the 36 deaths. These cases are never placed with lowered head, a mistake we formerly made.

Fifty-four cases required interference of some sort for obstruction of the airway. Aspiration of the membrane gave 1 case adequate relief. Intubation, done once or twice, relieved 5 cases but was unsatisfactory in 8 others. Tracheotomy was usually performed as a matter of choice, either because the tube to be used was too small or the inflammation and edema of tissue would quickly obstruct the tube's opening. Of a total of 48 who had required tracheotomy, 22 died. Of the fatal cases, 11 were of the "bull neck" type, 4 were laryngotracheal, and the remaining 7 had tonsillopharyngeal and laryngeal involvement.

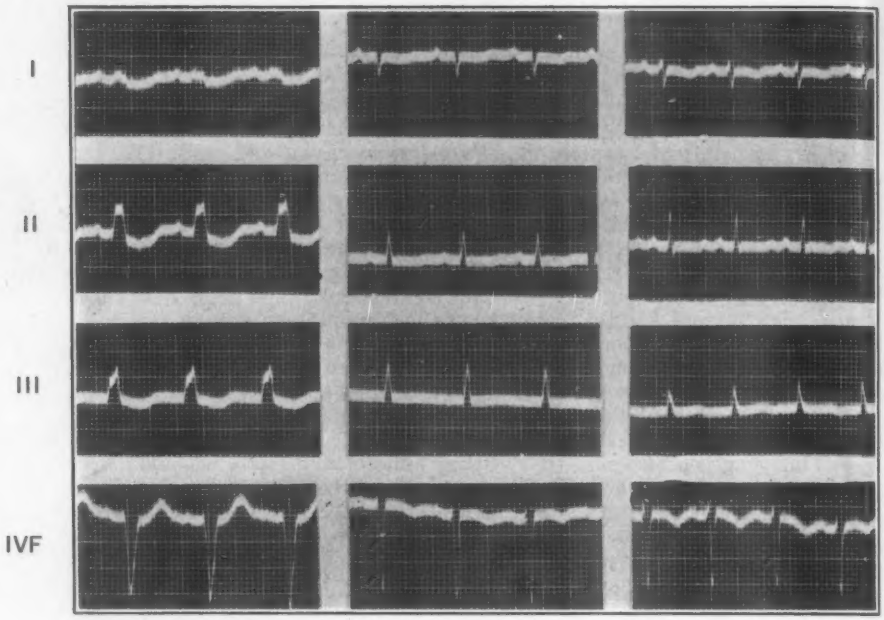

FIG. 1.—*A*, December 16, 8 days after onset, shows marked myocardial damage with bundle branch block of unclassified type. *B*, December 20: the bundle branch block has disappeared. Persistent evidence of myocardial damage as demonstrated by inverted T_1, low voltage T_2, and very small R, IVF. *C*, January 8, shows additional changes with presence of diphasic T_1, T_2, and the presence of R, I and R, IVF with increased elevation.

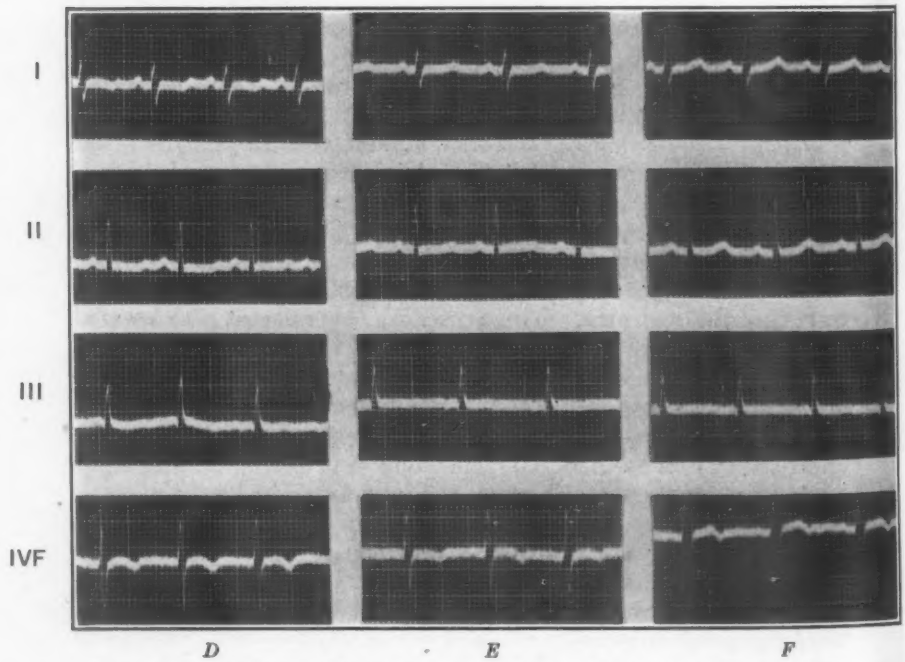

FIG. 2.—*D*, January 20, shows further elevation of R, I and R, IVF. *E*, January 28, shows a return of T_1 and T_2 to the upright position simulating a normal electrocardiogram. *F*, March 3, an essentially normal electrocardiogram.

Dr. S. Jesberg and Dr. A. Miller (Eye and Ear Hospital) from 1922 to 1927 have seen 6000 cases of which 503 were laryngeal. Of these, 25% died during the first 24 hours; and of the survivors, 22 ended in laryngeal stenosis of such degree as to demand more or less protracted treatment. In our series 5 patients had to have such treatment. Including these and others referred to them, Drs. Jesberg and Miller have treated 103 such cases with the following results: 6 deaths, 1 each from pneumonia, heart failure and lung abscess, and 3 of unknown causes; 9 still under treatment as of May 22, 1941, all greatly improved; 41 cured within 3 months; 13 cured within 6 months; 5 cured within 1 year; and 13 cured within 5 or more years. Most of these patients were treated by constant dilatation of the larynx by means of a section or core cut from an ordinary rubber urethral catheter pulled up into the introducer. These rubber sections were left in place for 2 or 3 weeks and replaced by larger ones. This method differs from other methods of indwelling dilators in that the cores are simply pieces of rubber catheters which may usually be introduced through the tracheotomy wound without making a large trough.

In 17 patients the stenosis was so great that before the dilators could be used and external tracheolaryngostomy had to be performed, in which the tracheotomy wound was extended to the upper limits of the stenosis, the scar tissue removed, and a trough formed by suturing the skin edges to the mucous membrane margins of the trachea. In 13 patients puncture cautery of the stenotic ring was done through the direct laryngoscope before the dilatations were begun.

Serum Reactions and Serum Sickness. There was 1 serum fatality noted in the 753 cases. The patient was 5 months old. Following a negative skin test, 20,000 units of antitoxin was given intramuscularly, at which time the temperature was 100.4°. Within 12 hours the temperature had risen to 106°, and the child died in 36 hours with a terminal temperature of 107°. Except for scant terminal bronchopneumonia there were no other complications. Unfortunately, permission for autopsy could not be obtained and the case was classified as probable serum reaction.

There were 181 cases (31.7%) out of 572 in which presence of serum sickness was noted; in 181 cases the record was incomplete in this respect. Fever, urticaria and serum arthritis were accepted as evidence of serum sickness. Table 4 shows the distribution by day of occurrence. The duration of reaction was 1 to 4 days and except for discomfort it presented no problem.

Miscellaneous Complications. The only other complication which occurred with any noticeable frequency was otitis media (15 cases). Pharyngeal paralysis which is reported so frequently in other hospitals[6] occurred in only 7 of the 753 cases, and 1 case of peripheral paralysis was noted. It is probable that cases of the latter type do not return to contagious disease wards, but are seen elsewhere.

The disease most commonly seen with diphtheria is scarlet fever, of which we saw 24 cases. In the children's ward of the tuberculosis unit there have been outbreaks of diphtheria, often starting from an indolent case of the nasal type. Interestingly enough, the University of California Department of Hygiene reports[1] that the cultures from this group were classified as of the gravis type.

TABLE 4.—INCIDENCE OF SERUM SICKNESS AMONG 635 CASES BY DAY OF ONSET OF REACTION.

Days.	Cases.	Days.	Cases.
1	13	13	1
2	20	14	4
3	5	15	0
4	8	16	2
5	15	17	0
6	18	18	2
7	22	19	0
8	22	20	0
9	22	21	1
10	11	27	1
11	9	Unk.	1
12	4		
		Total	181

Death and Its Associated Conditions. Of the 36 deaths, 22 were in cases which had required tracheotomy, but of these only 4 were due to the laryngotracheo-bronchial type. Death in 1 case was due to hemorrhage following accidental severing of an anomalous carotid artery. Twenty deaths were in cases of the "bull neck" type. Table 5 shows the more common forms of complications and related conditions seen in the 36 cases of fatal diphtheria.

TABLE 5.—COMPLICATIONS AMONG 36 DEATHS OF DIPHTHERIA.

	No. of cases
Bronchopneumonia	20
Toxic myocarditis, clinical and autopsy	18
Toxic purpura	5
Atelectasis	3
Emphysema:	
Subcutaneous	3
Mediastinal	1
Otitis media	2
Hemorrhagic nephritis	1

Autopsies were performed on 17 of the 36 deaths. The chief findings other than those of diphtheria *per se* were: bronchopneumonia in 12, myocarditis in 9, atelectasis in 4, otitis media, toxic nephritis and adrenal hemorrhage each in 2 and hemorrhagic nephritis in 1. The myocardial lesions found differed in no essential from those reported by Warthin,[11] and were described as varying degrees and combinations of cloudy swelling, mononuclear infiltration, fragmentation of muscle, parenchymatous degeneration and necrosis, polymorphonuclear infiltration and fibrosis.

Summary. 1. Of 753 cases of diphtheria, 36 (4.8%) died.

2. Males represented 48% and females 52%.

3. The age incidence is charted, showing 61% before 10 years.

4. Average duration of illness before antitoxin was given was 3.7 days. Greater duration is shown to increase hazard.

5. Distribution of lesions and increased mortality with greater extension are tabulated.

6. Dosage of antitoxin was 20,000, 30,000 and 40,000 units in 28% each of the total, with lesser and larger amounts in a few cases, given intramuscularly except to the very toxic.

7. Therapy as used in the Communicable Disease Unit of the Los Angeles County General Hospital is discussed.

8. Complications of myocarditis, bronchopneumonia, asphyxia and stenosis, and other miscellaneous conditions are considered and treatment outlined.

9. Summary of deaths and the associated conditions is presented.

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THE EFFECT OF KIDNEY POSITION ON RENAL BLOODFLOW AND FUNCTION.

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The piezometric* angle of the renal artery, as a factor determining renal bloodflow, was investigated. The importance of such angles in the regulation of arterial flow in other parts of the body has been emphasized by Swindle.[7]

Figure 1 shows how the renal circulation may be altered by changing the piezometric angle of the renal artery. With the renal artery elevated to Position A, the head pressure falls. At Position C the pressure increases instead.

* A piezometric angle is the angle between a tributary and the advancing blood stream in the mother artery.

The problem was approached in two ways: 1, pressure recordings were obtained from the cannulated renal artery of a dog while this vessel was made to form various angles with the aorta. 2, Diodrast clearance tests were done on several dogs with the renal artery at various angles.

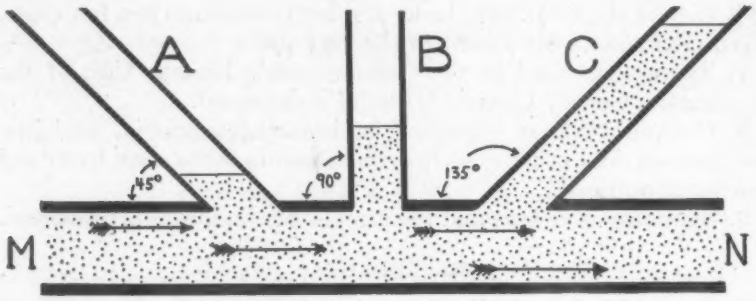

FIG. 1.—Pressure relationships in a system of tubes where the branches, *A*, *B* and *C*, form various angles with the main tube, *MN*, and fluid is traveling in the direction indicated. If *B* represents the approximate angle that the renal artery forms with the aorta, *MN*, and if the angle be changed to that of *A* or *C*, then the resultant head pressure of the renal artery will change as illustrated.

Methods. Seven dogs under nembutal anesthesia were used in this study. On the first dog, the right renal artery was cannulated and was connected with rubber tubing to a recording tambour. A 4% solution of sodium citrate was used as an anticoagulant. Tracings were obtained for various piezometric angles (Fig. 2). On the remaining animals a subcostal incision was made, so that the kidney could be exposed and ligated at the pedicle, including artery, vein, and ureter. The wound was then closed immediately to conserve body heat. Then, through a similar incision on the opposite side, the left kidney was exposed and the ureter was cannulated. An infusion of 1% Diodrast in physiologic saline was introduced at the rate of 20 drops per minute through a catheter inserted in an external jugular vein. For two periods of 60 minutes each urine was collected at 10-minute intervals and blood specimens were taken at the exact midpoint of each collection period. On Dogs 2, 3, 4 and 5 the kidney was unaltered in position during the first 60-minute period but during the second 60-minute period it was moved cephalad and held securely in this position by light packing. Precautions were taken to prevent compression of the renal artery, vein, and ureter. The angular change of the renal vessels was approximately 45 degrees. The procedure was reversed on Dogs 6 and 7. The kidney was elevated during the first period, and during the second period its normal position was restored. Systemic arterial blood pressures were taken several times during each experiment. Blood and urine were analyzed for iodine according to the method described recently by Alpert.[1]

Results. Figure 2 illustrates that a considerable reduction of the mean blood pressure and also of the pulse pressure occurred when the piezometric angle of the renal artery was relatively acute. Similarly Table 1 presents evidence that the plasma clearance averaged 35.6% less with the kidney elevated, and Table 2 shows that an almost identical reduction (30%) occurred when the figures, corrected to surface area, are compared with those of the control periods of the

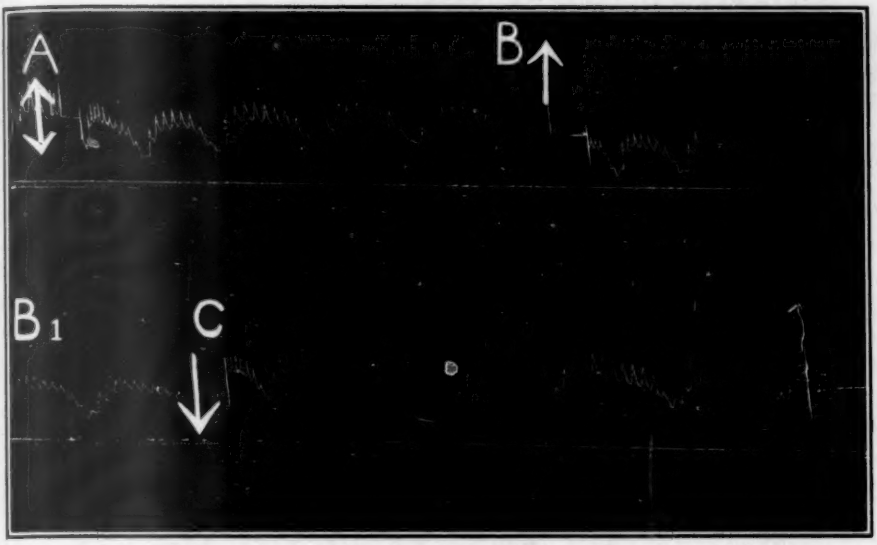

FIG. 2.—Effect on the mean blood pressure and the pulse pressure of the renal artery, when its piezometric angle is altered. *A*, with the renal artery at its normal position; *B*, with the renal artery elevated; B_1, continuation of *B*; *C*, with the renal artery lowered. The base line is a straight one and simply serves for comparison. Note that the mean and pulse pressures are reduced when the kidney is elevated and increased when the artery is lowered.

TABLE 1.—RESULTS OF DIODRAST CLEARANCE TESTS WITH THE KIDNEY IN (*a*) NORMAL AND (*b*) ELEVATED POSITION.

Each plasma clearance value is derived from a 1-hour test consisting of 6 urine collection periods of 10 minutes each, as described under Methods. The control period during which the kidney was in its normal position is indicated by (*a*) and the 60-minute period during which the kidney was elevated by (*b*).

Dog.	Weight (kg.).	Hematocrit (% cells).	Blood pressure (mm. Hg).		Plasma clearance (cc./min.).	Corrected to sq. m.	Reduction (%).
2 . . .	11.4	48.6	98	(*a*)	91.4	163.2	
		47.5	104	(*b*)	54.9	98.0	39.9
3 . . .	12.0	52.5	106	(*a*)	98.8	167.4	
		53.2	98	(*b*)	62.8	106.4	36.4
4 . . .	5.9	49.3	86	(*a*)	57.9	156.5	
		47.5	90	(*b*)	38.2	103.3	36.4
5 . . .	2.8	54.0	82	(*a*)	29.8	141.9	
		51.5	84	(*b*)	20.2	96.1	32.3
						Average	35.6

TABLE 2.—RESULTS OF DIODRAST CLEARANCE TESTS WHERE THE PERIOD OF KIDNEY ELEVATION PRECEDES THE PERIOD DURING WHICH THE KIDNEY WAS RESTORED TO ITS NORMAL POSITION. (*a*) AND (*b*) SIGNIFY THE SAME AS IN TABLE 1.

Dog.	Weight (kg.).	Hematocrit (% cells).	Blood pressure. (mm. Hg).		Plasma clearance (cc./min.).	Corrected to sq. m.	% improvement.
6 . . .	14.9	44.0	110	(*b*)	75.2	110.6	
		42.5	104	(*a*)	94.8	139.4	26.0
7 . . .	22.0	44.0	118	(*b*)	96.2	109.3	
		43.5	110	(*a*)	112.5	127.8	16.9
						Average	21.4

first group of dogs. However, in the second group an improvement of only 21.4% resulted when the kidney position was restored. In this regard, the observation was made in all cases that the kidney became markedly congested and increased in size shortly after it was elevated.

It will be noted that the volume output of urine in Dogs 3, 4 and 5 was reduced from 0% to 51.9% after kidney elevation (Table 3).

TABLE 3.—ILLUSTRATES THE EXACT QUANTITY OF URINE ELABORATED BY EACH DOG DURING EACH 10-MINUTE PERIOD OF THE ENTIRE EXPERIMENT.

The figures in italics represent the period during which the kidney was elevated.

Time (min.)	Urine volume in cubic centimeters.					
	2.	3.	4.	5.	6.	7.
0						
10 . . .	3.4	5.8	6.6	8.2	*3.8*	*4.2*
20 . . .	3.6	6.0	7.4	8.0	*3.3*	*3.9*
30 . . .	4.0	7.4	8.6	8.2	*3.1*	*3.7*
40 . . .	3.8	5.8	8.0	8.4	*3.0*	*3.2*
50 . . .	3.9	6.0	9.1	7.2	*2.9*	*3.1*
60 . . .	3.8	5.6	8.1	6.8	*2.4*	*2.8*
	22.5	36.6	47.8	46.8	*18.5*	*20.9*
	Interval During Which Piezometric Angle Was Changed.					
80						
90 . . .	*4.8*	*3.4*	*6.5*	*4.2*	3.8	3.1
100 . . .	*4.3*	*3.2*	*6.9*	*4.2*	3.9	3.0
110 . . .	*3.8*	*3.4*	*6.6*	*4.3*	4.4	3.2
120 . . .	*3.8*	*3.0*	*6.3*	*3.9*	4.0	2.8
130 . . .	*3.4*	*3.3*	*5.7*	*3.3*	4.6	2.4
140 . . .	*3.0*	*3.2*	*5.3*	*2.6*	3.7	3.2
	23.1	*19.5*	*37.3*	*22.5*	24.4	17.7

Comparable reductions did not occur in any of the other animals except Dog 6, but the urine output nevertheless diminished progressively during the elevation period in all of the dogs.

Discussion. It has been demonstrated in this investigation that renal bloodflow can be reduced considerably by elevating the kidney. The mechanism responsible is undoubtedly a simultaneous reduction of the mean blood pressure and also the pulse pressure. Friedman, Sugarman and Selzer[3] state that a reduction of both mean and pulse pressure is invariably followed by renal vasodilatation and a fall in the glomerular filtration rate. It can be safely assumed, therefore, that glomerular filtration in these dogs was also reduced. That this occurred is further substantiated by microscopic sections which reveal that the glomerular capillaries of elevated kidneys appear considerably less filled with blood than those of normal, control kidneys.

Before results of this nature may be applied clinically, it is necessary to establish that the kidney of human beings is not fixed and identical in position in all individuals. Moody and Van Nuys[5] claim that the kidneys in most healthy men and women have a con-

siderable range of mobility, the range of excursion in women varying between 0.1 to 9.3 cm. They conclude that the kidney is definitely a floating organ. Acknowledging, therefore, that variability of position exists, it is obvious that there is also variability of the piezometric angles of the renal artery. This may well be an anatomic basis of what is commonly spoken of as "a predisposition toward hypertension."

Woodruff and Milbert[3] have demonstrated that kidney position is altered by pregnancy and that as gestation progresses, the kidney is gradually raised cephalad by the advancing uterus. Therefore, the distinct change in renal bloodflow which follows when the piezometric angle of the renal artery is reduced may be the factor which initiates the clinical picture of toxemia of pregnancy. Since the degree of renal embarrassment depends on the height to which the kidney is raised, there are factors present in the incidence of toxemia which indicate that in such cases the kidney may be elevated relatively higher than in otherwise normal pregnancies. For instance, Stander[6] notes that toxemia is more frequent in primiparæ rather than in multiparæ and the uterus is commonly overdistended as with multiple pregnancy or even polyhydramnios. Interesting in regard to the observation that primiparæ are more susceptible is the notation by Griefenstein[4] that recurrences in previously eclamptic women average only 2.6%. It is possible to explain these apparently unrelated facts on a physiologic basis. Primiparæ unquestionably have greater tone to their abdominal musculature, they therefore carry their pregnancy relatively high and the pressure displacing the kidneys is conceivably greater. On the other hand, multiparæ with their relaxed abdominal musculature permit greater forward protrusion of the pregnancy with a consequent diversion of the otherwise cephalad pressure. In addition, the presence of an overdistended uterus still further contributes to the displacement of the kidneys.

Corcoran and Page[2] in their study of renal function in late toxemia of pregnancy discovered that those cases uncomplicated by previous hypertension have without exception a low filtration rate even in the presence of a normal or decreased total renal bloodflow. They concluded by a process of elimination that the primary cause of the diminished filtration rate is increased resistance of the glomerular filter. In view of the fact that the hydrostatic pressure of the glomerulus can be reduced so markedly by elevation of the kidney it would appear more correct to assume that derangement of the glomerular function occurs secondarily.

Summary. 1. Renal bloodflow is profoundly reduced when the piezometric angle of the renal artery is made relatively acute.

2. It is possible that the anatomic basis of predisposition toward hypertension lies in the extreme variability of the position of the kidney.

3. The deranged renal function of uncomplicated late toxemia of

pregnancy may be the result of relatively high elevation of the kidney during gestation, depending on body type and abdominal muscle tone.

Acknowledgment is made to Dr. Eben J. Carey, Dean and Director of the Department of Anatomy at Marquette University Medical School, for providing the facilities and material which made this investigation possible; to Dr. P. F. Swindle, Professor of Physiology, for his many valuable suggestions; to Dr. J. C. Grill, Associate Professor of Pathology and Bacteriology, for examining the microscopic sections. Gratitude is also expressed to Mr. E. Haushalter for his assistance in the operative procedure.

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GIANT FOLLICULAR LYMPHOBLASTOMA (GIANT LYMPH FOLLICLE HYPERPLASIA).*

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Since 1925, when Brill, Baehr and Rosenthal[6] first called attention to the pathologic picture now generally referred to as giant follicular lymphoblastoma, a number of reports have appeared in the literature dealing with this condition. More recently there have been several excellent publications in which the discussions of the clinical and pathologic aspects were based on large series of cases. The purpose of this report is to stress certain points in connection with this disease entity rather than to add to the ever-growing number of cases.

We feel that, although the condition is well known to and easily recognized by most pathologists, it is still thought of only too rarely by the clinician. The importance of its early recognition—and this can be done only by biopsy and histologic study of the lymph node removed—becomes apparent when one knows how remarkably radiosensitive these tissues are, particularly in their early stages. However, it must be borne in mind that recurrences are

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common and that after a number of years the disease may take a malignant form and terminate as lymphosarcoma, lymphatic leukemia or Hodgkin's disease.

Definition. Giant follicular lymphoblastoma is a relatively benign disease of the lymphatic system. It is characterized by: lymphadenopathy, which is due to enlargement of the follicles of the involved nodes; splenomegaly in most cases; a normal blood picture; the absence of anemia and cachexia; a long course; and a prompt response of the lymph nodes and spleen to Roentgen ray therapy in the early stages of the disease.

History. In 1901 a case of "simple hyperplasia" of lymph nodes was reported by Becker[5] which apparently showed the histologic picture of the disease entity under consideration. In the next 20 years a few other investigators[7,8,12] described the condition. However, it was not until Brill and his coworkers reported their 2 cases in 1925 that the attention of the medical profession in this country was drawn to this disease. They considered it a benign lymphadenopathy and applied the name, "giant follicle hyperplasia." Two years later Symmers[14a] reported 3 additional cases. In that same year Baehr and Rosenthal[2] reported a total of 6 cases, but now described the condition as "malignant lymph follicle hyperplasia of spleen and lymph nodes." They regarded it as a clinical and pathologic entity distinct from lymphosarcoma.

By 1931, Baehr, Klemperer and Rosenthal[3] were convinced that the disease could be differentiated from simple follicular hyperplasia of inflammatory nature. Furthermore, they had followed some of their cases long enough to observe that later in the course of the disease, the follicles fused, the capsule became infiltrated and the surrounding tissue invaded. This forced them to the conclusion that the condition was a form of lymphosarcoma. They therefore proposed the name "follicular lymphoblastoma," which is now in fairly general use. The above-named group continues to maintain this view.[1]

The inflammatory or toxic origin of the disease has been championed by Symmers[14b] who, in 1938, reviewed 32 cases, and applied the term "giant follicular lymphadenopathy with or without splenomegaly."

Thirteen seen cases and 59 collected from the literature were studied (1940) by Baggenstoss and Heck.[4] More recently, Gall, Morrison and Scott[9] reviewed 63 cases diagnosed by biopsy or necropsy.

Pathology. Our purpose is to deal with the clinical aspects of the disease and its pathogenesis. In order to clarify our views we shall discuss briefly the pathologic changes encountered. The disease appears to have a multicentric origin, so that enlarged lymph nodes may be found in various parts of the body. These may attain great size, the nodes remaining discrete and firm in consistency. Gener-

ally the spleen is markedly enlarged. Involvement of various other organs has been reported. As the reported cases accumulate it becomes evident that lymphatic tissue of almost any organ in the body may be the seat of such lesions.

The enlargement of the lymph nodes is due to a marked increase in the number and size of the lymph follicles. These are usually diffusely scattered throughout the node and may reach tremendous size. As the disease progresses the follicles may fuse and the histologic picture change so completely that no trace of the follicular structure may be found.

Similarly, the splenic enlargement is due to an increase in the number and size of the Malpighian corpuscles. When perinodal tissue is involved, the same follicular arrangement is seen as within the nodes themselves.

The primary change within the lymph follicles themselves appears to be the formation of large "germinal centers" surrounded by a rim of darker staining adult lymphocytes. The enlargement of the follicles and their increase in number causes compression of the interfollicular structures. Gall and his associates recognize four types of lesions, dependent largely upon the state of preservation of the follicles, and express the view that they probably represent progressive phases in the pathogenesis of the disease.

Clinical Course. As in most diseases of the lymphatic system, so in giant follicular lymphoblastoma the clinical picture is very variable. The disease usually makes its appearance in the third or fourth decade of life. The first manifestation is generally an enlargement of regional lymph nodes, axillary, inguinal, cervical, retroperitoneal, and so on. The involvement may be more or less generalized when the patient first comes under observation. Splenomegaly occurs in a fair percentage of cases, variously given as 33% to 61.1%.

It is remarkable that the patient has a feeling of well-being even when the lymphadenopathy is widespread. Cachexia is usually absent and anemia a relatively rare occurrence. In the early stages the blood picture may be entirely normal. The disease runs a protracted course. The average duration is 5 to 6 years. Two cases referred to by Baggenstoss and Heck were alive after 17 years. Ascites and hydrothorax are not infrequently encountered. Osseous, cutaneous, pulmonary, genito-urinary, gastro-intestinal and tonsillar involvement have been reported.

All investigators agree that in the early stages of the disease the lymph nodes show a remarkable sensitivity to the Roentgen rays. The lymph nodes may no longer be palpable and the spleen may be restored to its normal size after a few exposures. However, as the disease progresses, this radiosensitivity diminishes and finally there is no response to Roentgen ray therapy. After repeated remissions, the disease may terminate as lymphosarcoma, lymphatic leukemia

or Hodgkin's disease. Thus far, no cases have been reported as cured.

Case Reports. Two cases seen by us are briefly summarized here to illustrate the early clinical manifestations.

CASE 1. Mrs. B. R., aged 57, was admitted to the Medical Service of the Beth Israel Hospital on February 13, 1940, complaining of fatigue of 1 month's duration and pain in the left leg for 1 week. During the 3 years prior to admission she had been examined repeatedly because of abdominal distress and eructations attributed to a proven cholelithiasis. She was examined 1 week before her admission to the hospital and found to have a mass in the abdomen. Her past history and family history were non-contributory.

On admission to the hospital her temperature was 99.6° but reached normal the next day and remained so. There was slight conjunctival icterus. A soft systolic murmur was heard at the apex. The lungs were clear. The superficial veins in the suprapubic region were somewhat distended. A huge mass filled the left side of the abdomen and flank, the medial border of the mass extending to the mid-line, the lower edge to the iliac crest. The mass moved somewhat on respiration and was ballotable. The edge of the spleen could be felt just below the costal margin and distinct from this tumor mass. The liver could not be palpated. One small non-tender node was present in the right supraclavicular region. Several discrete, non-tender lymph nodes were palpated in both inguinal regions. They were more numerous on the left side where one larger node, about $\frac{1}{2}$ inch in diameter, could be felt. From the vaginal examination it would appear that the abdominal mass did not arise from any of the pelvic organs. On digital rectal examination a firm, non-tender mass could be felt extrinsic to the rectum.

A blood count showed 4,500,000 red cells and 90% hemoglobin. There were 6400 white blood cells with a normal differential count including 3% eosinophils. The blood chemistry figures were normal. Blood Wassermann test was negative. Repeated urine examinations were negative except for occasional pus cells in non-centrifuged specimens. The stools showed no occult blood.

Roentgenologically, the colon was found to be normal in position and normal in contour except for diminution of the lumen of the descending portion. The gall bladder was long and flexible and contained numerous radio-opaque calculi. An intravenous pyelogram showed normal kidneys, pelves and calyces. There was evidence of extrinsic pressure on the upper surface of the bladder. On the flat film of the abdomen the liver appeared normal in size and the shadow of a small spleen could be seen very clearly. A large, moderately opaque mass occupied the greater portion of the left side of the abdomen. This mass did not displace the left kidney, nor encroach on the left psoas shadow. Roentgen rays of the chest showed no evidence of mediastinal involvement.

On February 26, 1940, a lymph node was removed from the left inguinal region. Microscopic examination of this node showed tremendous follicles resembling large "germinal centers" and surrounded by a zone of mature lymphocytes. In some places the sinusoids and lymphocytes were markedly compressed by the giant follicles (Fig. 1).

The patient received 9 Roentgen ray treatments in all. After the sixth exposure a definite and marked decrease in the size of the abdominal mass could be noted. At the time of her discharge from the hospital, on March 24, 1940, the abdominal mass was no longer palpable. A few very small lymph nodes persisted in her left inguinal region and one in the left supraclavicular region.

Up to the present time, February 1942, the patient has continued in good health and has shown no recurrence of the adenopathy.

CASE 2. Mrs. Y. S., aged 54, was admitted to the hospital on April 28, 1941, because of a slight painless swelling on the left side of the neck of 2 months' duration. There were no other complaints. There was nothing of note in her past or family history.

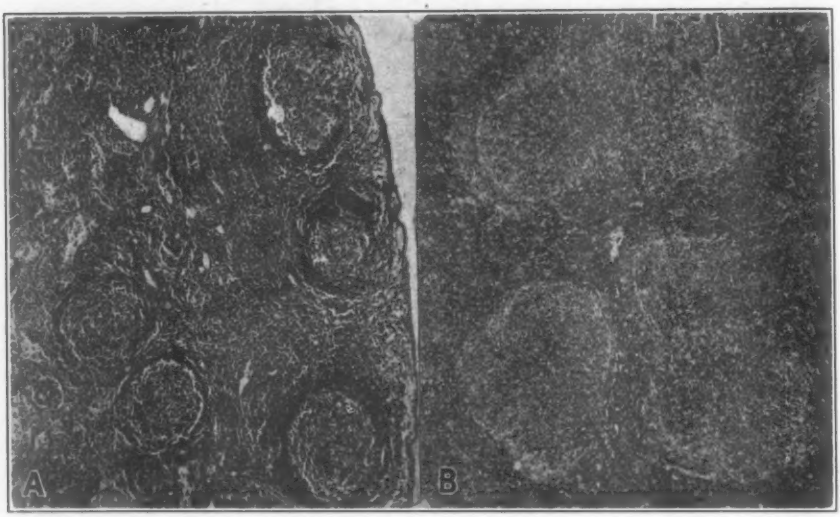

FIG. 1.—**A**, Section of a "normal" lymph node with large, pale staining centers surrounded by a rim of adult lymphocytes. The lymph follicles are distinctly separated. **B**, Markedly enlarged follicles with compression of the interfollicular structures (Case 1). (Same magnification as that used in *A*.)

On admission to the hospital she did not appear acutely or chronically ill. Her temperature was 100.6°, and subsequently ranged between 98.6° and 99.8°. A firm, non-tender, freely movable mass about 1¼ inches in diameter was present in the left posterior cervical region. This was not attached to the skin or the underlying structures. There were also a few small, discrete lymph nodes in the anterior triangle of the left side of the neck and 2 small nodes in each axilla. There was no other apparent adenopathy. The liver and spleen could not be palpated. The remainder of the physical examination was essentially normal.

Blood studies showed 4,550,000 red cells with 80% hemoglobin. The white cell count ranged from 3100 to 3300. There was a normal differential count with 3% to 4% eosinophils. Blood chemistry was normal. The blood Wassermann test was negative. Urines showed a heavy trace of albumin and many pus cells with occasional pus clumps.

Roentgen ray examination of the chest showed some calcified nodes in both hilar regions but no mediastinal involvement.

On May 3, 1941, a lymph node was removed from the left supraclavicular region. Microscopic examination of this node showed the early changes of giant follicular lymphoblastoma (Fig. 2).

The patient was discharged on May 9, 1941, and referred for Roentgen ray therapy. In all, she received 15 treatments, the last one on June 16, 1941. On June 9, 1941, it was noted that the size of the lymph nodes had

diminished. By June 16 the nodes in the right supraclavicular region were no longer palpable. When seen on November 14, the patient was generally well. There were no palpable cervical, axillary or inguinal nodes. The liver and spleen could not be palpated.

FIG. 2.—Tremendous enlargement of the follicles which are surrounded by darker staining, adult lymphocytes compressed into a thin rim. There is also fusion of the follicles at some points (Case 2).

Comments. Despite careful studies of biopsy and autopsy material there still exist differences of opinion as to the classification and pathogenesis of giant follicular lymphoblastoma. Most investigators agree that this condition represents merely a stage in the pathologic changes occurring in the lymphatic tissue, since sooner or later this relatively benign disease terminates as a lymphosarcoma, or lymphatic leukemia. A terminal picture of Hodgkin's disease has also been suggested by Symmers.[14b]

It has been suggested by Ross[13] that this condition is a hyperplasia of undifferentiated cells with unrestricted potentialities for differentiation. He regards it as a "lymphoid reticulosis." Jackson[11] also looks upon it as an early form of malignant lymphoma which may become transformed into any one of the recognized types. Symmers[14b] maintains his original view that giant follicular lymphoblastoma is most likely of inflammatory or toxic origin. He feels it is "capable of direct transformation into a polymorphous cell sarcoma;" he holds that it may also have superimposed upon it the histologic features of Hodgkin's disease by the deposition in the modified lymph nodes of megakaryocytes from the bone marrow. In like fashion it may become associated with the changes of lymphatic leukemia. These views are at variance with those of Baehr

and Klemperer who state that their experiences suggest "that follicular lymphoblastoma may represent a borderline condition between lymphosarcoma and lymphatic leukemia, just as in its early stages the disease may seem to represent a transition between hyperplasia and lymphosarcoma."[1]

It has long been recognized, and recently stressed by one of us,[10] that in different diseases involving the lymphatic tissue different structural components of the lymph nodes are primarily involved. So, for example, we find that in Hodgkin's disease the endothelial portion is the seat of the disorder. There are other diseases of the lymphatic system in which the involvement is fundamentally one of the lymphocytic tissue of the lymph glands. Such is the case in lymphatic leukemia. In still others the lymphocytic and the reticular structures are involved, giving the pathologic picture of lymphosarcoma and reticulum cell sarcoma. In giant follicular lymphoblastoma the "germinal centers" of the secondary follicles are the point of departure of the pathologic process. In inflammatory diseases, such as tuberculosis and syphilis, all structures within the lymph nodes usually show changes.

It is generally true that the patient in whom a diagnosis of lymphosarcoma is established by biopsy will continue to have lymphosarcoma until his death. The same holds for Hodgkin's disease and lymphatic leukemia. Our concept is that in giant follicular lymphoblastoma the groundwork for the terminal picture is laid down early in the disease, despite the fact that in the very earliest stages this cannot at present be recognized by the pathologist.

We feel that, whatever the etiologic factor, the disease starts in the so-called "germinal centers" of the lymph follicles. At this stage it is still reversible, but it may terminate as lymphosarcoma, lymphatic leukemia or, in rare cases, Hodgkin's disease.*

A knowledge of the course the disease may take and the fatal termination which may be anticipated is of practical importance. It is possible that, by continuing Roentgen ray therapy during the periods of remission, the development of the malignant phase may be retarded or prevented.

Conclusions. 1. The pathologic changes encountered in giant follicular lymphoblastoma are described briefly.

2. The clinical course of the disease is outlined and 2 illustrative cases are cited.

3. The fact is stressed that the disease may terminate with the picture of lymphosarcoma, lymphatic leukemia or, rarely, Hodgkin's disease.

* We do not know personally of any well-authenticated cases of giant lymph follicle hyperplasia terminating in Hodgkin's disease; nor is it conceivable, except as coincidence, unless one accepts the cells that compose the pale centers of the follicles as identical with the endothelioid cells of Hodgkin's disease. The nature of the cells of the pale centers, to be sure, still remains in doubt.—EDITOR'S NOTE.

4. The concept that the groundwork for the terminal picture is laid down in the very beginning of the disease is offered.

5. It is suggested that Roentgen ray therapy during the remissions in the course of the disease may retard or prevent the development of the malignant phase.

We wish to thank Dr. Alfred Plaut for the histologic preparations.

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ACUTE MYOCARDIAL INFARCTION WITHOUT DEVIATION OF THE S–T SEGMENT IN THE ELECTROCARDIOGRAM.*

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Among the deviations from the classical pattern in recent myocardial infarction[2,4,7,11–13] we have found a type for which no proven explanation has been offered. It is the type which resembles the classical curve but lacks the characteristic sign which is part of the expected record, namely, an elevation of the S-T segment, the so-called "high take off" of the T-wave in the older literature.

The case presented in this report is the only one with autopsy in our series of 8 cases with recent myocardial infarction in which the acute stage showed no S-T deviations or only an S-T depression. This electrocardiogram in the autopsied case was found to be associated with recent infarction which did not extend to the epicardium. The explanation offered by Boyd and Scherf[5] and by Ashman and Hull[1] thus seems to be substantiated.

* Aided by the A. D. Nast and the Emil and Fanny Wedeles Funds for Cardiac Research.

Case Report. A 63-year-old female was admitted to the Orthopedic Service (Dr. D. H. Levinthal) of this hospital on June 15, 1941 complaining of severe pain in the right hip joint. One hour before admission she had stumbled in her room at home, had fallen to the floor and was unable to rise. Several months before she had complained of pain in the right hip, and Roentgen-ray had revealed a cystic lesion of the neck of the right femur. A review of systems was essentially negative. The past history did not reveal any symptoms indicative of cardiovascular disease.

On admission the temperature was 98.6° F., the pulse 96 and regular, respiration 22, blood pressure 140/90 mm. Hg. Physical examination showed a normally developed and well nourished female, in evident severe pain. Heart, lungs and abdomen showed no abnormal findings. The right leg appeared shorter than the left. A Roentgen-ray picture revealed a pathologic fracture of the neck of the femur at the level of the lesser trochanter. Russel traction was applied, and morphine administered for pain. Laboratory findings: glucose 97 mg. per 100 cc., N.P.N. 38 mg. per 100 cc., uric acid 4.4 mg. per 100 cc., calcium 9.9 mg. per 100 cc., phosphorus 2.6 mg. per 100 cc., phosphatase 2.9 units. The blood count showed R.B.C. 4 million, W.B.C. 10,250 with 70% neutrophils. There was some albumin in the urine and a few granular casts were found on microscopic examination.

The Russel leg traction was not satisfactory, and so an attempt was made on June 24, 1941, to reduce the fracture under pentothal anesthesia, but the Roentgen-ray on the following day revealed the fragments still in poor position. Reduction was attempted again on June 28 with little success. The patient began running a low grade fever and on July 3 a diagnosis of bronchopneumonia was made and sulfathiazole therapy started. A chest film showed an area of haziness adjacent to the apex of the heart. An electrocardiogram (Fig. 1*A*) was taken. On July 7 the Roentgen-ray revealed the pneumonic process to be resolving. Aspiration biopsy from the fracture site showed blood inflammatory cells and occasional giant cells. On July 15 curettement of the bone cyst was carried out under gas anesthesia. A Smith-Peterson nail was introduced to unite the bone fragments. The immediate postoperative condition was excellent.

Suddenly, on July 17, the temperature rose to 102° F., the pulse to 120, the patient became markedly dyspneic and cyanotic, the blood pressure dropped to 85/55 mm. Hg., and the W.B.C.'s rose to 20,000. The R.B.C.'s had fallen to 2,700,000. Signs of bilateral bronchopneumonia were present. The patient received 50 cc. of 5% sodium sulfathiazole intravenously and 2000 cc. of glucose and saline by clysis.

On July 18 the condition appeared unchanged; temperature 103.6° F. A transfusion of 250 cc. of blood was administered, followed by 1000 cc. of 2.5% glucose.

On July 19 an electrocardiogram was taken (Fig. 1*B*). The blood pressure then was 82/70 mm. Hg. A blood transfusion of 250 cc. was repeated and 2000 cc. of 5% glucose were given by venoclysis.

On July 20 the patient's condition was "almost terminal." Cheyne-Stokes breathing, marked cyanosis was present, the temperature was 103° F., the blood pressure 92/80 mm. Hg. Again, 500 cc. of blood and 2000 cc. of 5% glucose were given.

On July 21 the third electrocardiogram was taken (Fig. 1*C*). Another 500 cc. blood transfusion and 2000 of 10% glucose were administered. The patient died the following morning.

At no time during her hospital stay did she receive digitalis.

Autopsy Findings. Pathologic diagnosis: Myxomatous central osteochondroma of the right femur with subtrochanteric fracture; severe coronary arteriosclerosis and atheromatosis of the aorta; recent thrombus in the

anterior descending branch of the left coronary artery; recent myocardial infarct of the anterior wall of the left ventricle and interventricular septum; mural thrombi in the left ventricle; terminal endocarditis superimposed on an old endocarditis of the mitral valve; passive hyperemia of the liver; bilateral hydrothorax; acute purulent bronchitis; recent bronchopneumonia of the right upper lobe; fibrosis and passive hyperemia of the spleen; arteriosclerotic scars of the kidneys; foci of old encephalomalacia.

Gross examination of the heart: The heart weighs 225 gm. The epicardium appears normal. The left ventricle is soft. The mitral valve is thickened and shows a few minute glistening verrucæ along the line of closure. The valve circumferences measure: tricuspid, 11 cm.; pulmonic, 7 cm.; aortic, 7 cm.; mitral, 8.8 cm. On section the myocardium of the anterior wall of the left ventricle and distal portion of the anterior septum shows large yellow patches sharply outlined against the remaining dark-brown muscle, especially towards the endocardial aspect (Fig. 2, *A*, *B*). They involve 0.5 to 0.75 cm. of the thickness of the myocardial wall and extend, in a vertical dimension, from about 1.5 cm. below the origin of the anterior descending coronary artery to the apex; horizontally, the anterior half of the septum and the medial 2 to 3 cm. of the anterior wall of the left ventricle are involved. The infarct comes closest to the epicardium in the anterior portion of the septum, becoming more subendocardial as it is followed laterally in the anterior ventricular wall. Friable grayish-pink mural thrombi adhere to the endocardium near the apex. The left ventricle is dilated and the ventricular wall measures 0.8 cm. in thickness. The right ventricular wall measures 0.2 cm. in thickness and shows fatty infiltration. The coronary ostia are patent; their lumina are narrowed by many yellow plaques. Proximal to an almost total arteriosclerotic occlusion of the left anterior descending is a gray-red slightly attached thrombus about 1 cm. distal from the origin of the artery. The right coronary is moderately narrowed.

Microscopically, there are large areas of deep-staining and granular myocardial fibers with faded or absent nuclei. In and around these areas are numerous neutrophils with an occasional extravasation of erythrocytes. Adherent to the endocardium are a few masses of recent thrombi containing some fibroblasts and a few capillaries. The infarcted areas appear in various sections to involve predominantly the inner half to two-thirds of the wall (Fig. 2*C*). Occasional small foci of necrotic fibers are seen at a distance of approximately one low-power field from the epicardial surface. The epicardial fat contains a loose scattering of monocytes.

Anterior descending coronary artery: The intima is markedly thickened by fibrous connective tissue containing many acicular spaces, foam cells and areas of calcification. The small lumen is filled by a recent laminated thrombus with a few invading fibroblasts.

Mitral valve: The valve is thickened by cellular fibrous connective tissue. On one aspect is a small patch of adherent fibrin, on the opposite aspect is a subendocardial area of loose fibrous tissue containing mononuclear cells.

Addendum. While this article was in press, a case similar to that reported above was observed in which a diagnosis of subendocardial infarction was made clinically on the basis of the electrocardiogram shown in Figure 3. This was confirmed at autopsy. The characteristic changes are shown in the chest leads. In the limb leads the possibility of a concordant type of left ventricular preponderance or of a transitory coronary insufficiency would have to be entertained. However, in view of the chest leads, the diagnosis of recent subendocardial myocardial infarction was favored.

Necropsy. The heart weighed 425 gm., the right auricle and ventricle were dilated and the left ventricle was hypertrophied. The endocardium

of the left ventricle was shaggy. In the inner two-thirds of the myocardium of the left ventricle, there was grayish-white streaking and stippling with pin-point hemorrhages, and the architecture was obscured. These changes involved the interventricular septum, and the anterior wall and the inferior aspect of the posterior wall. As in the first case, the architecture of the outer rim of the myocardium was apparently unaltered. The coronary arteries were moderately sclerotic, the anterior descending branch of the left coronary artery was completely occluded by a recent thrombus about 4 cm. from its point of origin.

Electrocardiogram. The first record (Fig. 1*A*) (taken on July 3, 1941) shows a regular sinus rhythm at a rate of 90. There is a left axis shift. The S-T segment is slightly depressed in Leads I and II, however, it is not below the level of the P-Q segment. T_1 and T_2 are upright, T_3 is small and inverted. Lead CF_2 is normal, CF_4 shows a slight depression of the S-T segment. The record was interpreted as probably within normal limits.

The second record (Fig. 1*B*) (taken on July 19, 1941) shows a sinus tachycardia with a rate of 120. There is a decrease in voltage both in the limb and chest leads. The QRS in CF_2 is now entirely inverted. The S-T segment is slightly elevated in CF_2 and no longer depressed in CF_4. T is smaller in both chest leads. The electrical systole (QRST interval) is prolonged, measuring 0.34 sec. instead of the expected 0.27 ± 0.04 sec. The record was interpreted as suggestive of an atypical anterior wall infarction and a repeat record was requested within 48 hours. This interpretation was based entirely on the changes in CF_2, since neither the limb leads nor the generally favored apical lead (in our case identical with CF_4) were suggestive of infarction.

The third record (Fig. 1*C*) was taken 2 days later (July 21, 1941) and 1 day before death. The heart rate is slower (100); there is some further decrease in voltage in the limb leads. S-T is now definitely depressed in Lead I and T_1 is almost isoelectric, T_2 is small and diphasic; T is smaller in CF_2 and is now inverted in CF_4. These changes confirmed the impression of an atypical recent myocardial infarction.

Comment. It has been shown conclusively that elevation of the S-T segment in cases of pericarditis is due to involvement of the uppermost (nearest epicardium) layers of the myocardium.[3,10] Recent experiments[5] suggest that changes confined to the subendocardial layers are not reflected in the electrocardiogram in the same way as changes in the subepicardial layers,[5,6] and that elevation of the S-T segment appears to be associated with involvement of the subepicardial myocardium only. In the light of these experimental findings, the question presents itself whether electrocardiograms in acute myocardial infarction with absence of S-T elevation are due to a peculiar location of the necrosis which leaves the subepicardial muscle free. [The accumulated knowledge about the separate layers of the ventricular musculature, with distinguishable electrocardio-

graphic patterns, blood supply and intramyocardial Purkinje fibers, now demands attention in any consideration of relationships between myocardial infarct and the electrocardiogram (see Robb and Robb: Am. J. Med. Sci., **197**, 7, 18, 1939, and Lowe, F. E.; Am. Heart J., **21**, 326, 1941). We know that the authors are aware of this knowledge, but as they have not considered it in their text, we wish to call attention to it here.—Ed. note.]

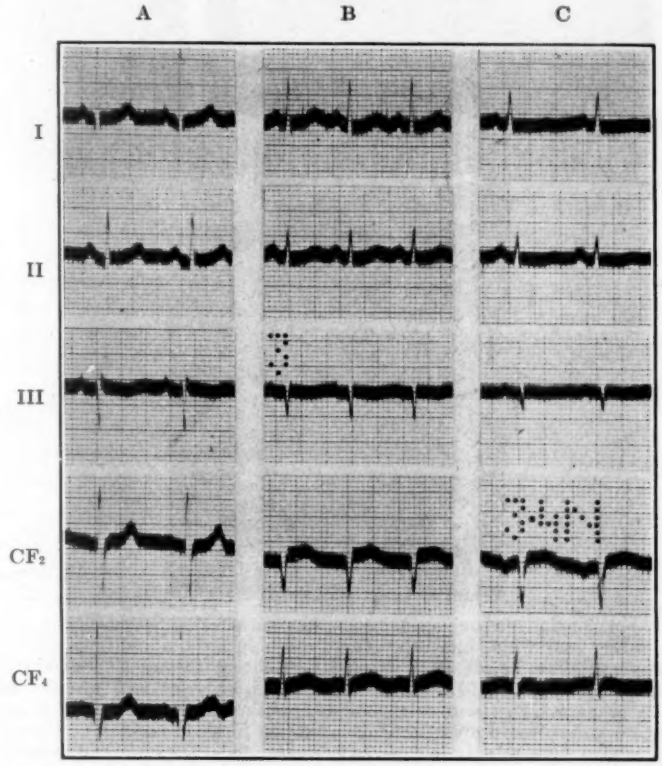

Fig. 1.—Five lead electrocardiograms of the patient. Record A, taken on July 3, 1941; B, on July 19; C, on July 21.

Gross and microscopic examination of the heart in our case showed a very recent infarct of the anterior wall of the left ventricle with predominant involvement of the subendocardial layers, the subepicardium being practically uninvolved. The infarct was considered typical in location and size for such located infarcts except for failure to extend to the epicardium.

According to the criteria of Mallory, White and Salcedo-Salgar[8] the histologic findings of recent necrosis, neutrophilic infiltration predominantly interstitial but occasionally more diffuse, and only the rarest evidence of phagocytosis or new capillary or fibroblast

formation, together set the estimated ages of the various observed areas of the infarct between 2 and 5 days. These postmortem findings, therefore, correspond to the lesion postulated for this variety of atypical electrocardiogram.

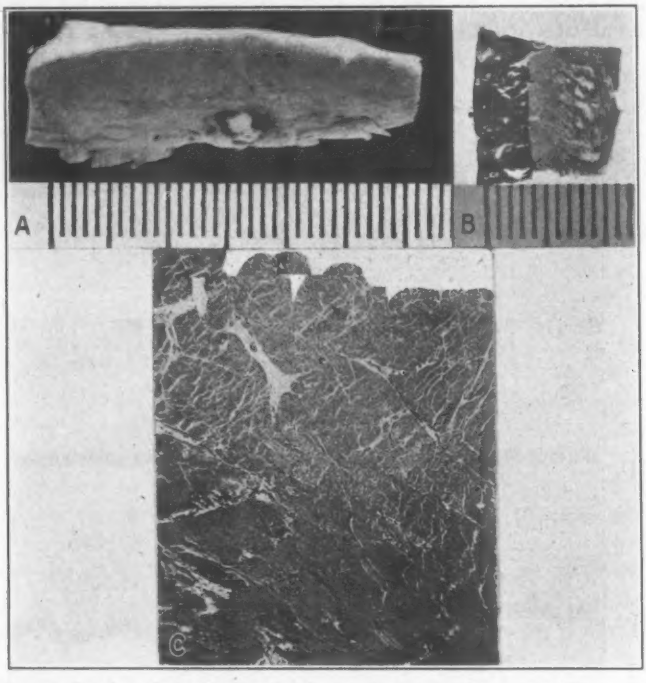

FIG. 2.—*A*, Section through unstained anterior wall of left ventricle. Note outer (upper) darker zone which indicates uninvolved myocardium and inner lighter zone indicating infarction. Note dark fragment of mural thrombus adherent to the endocardium (ruler in mm.). *B*, Section through anterior wall of left ventricle (Sudan IV preparation). Note deeply stained pericardial fat, mid-zone of uninvolved myocardium and subendocardial zone of infarction (ruler in mm.). *C*, Photomicrograph of section through anterior wall of left ventricle. Note layer of epicardial fat (faintly shown at very top of photograph), lighter staining uninvolved myocardium and darker stained zone of infarct. (Iron-hematoxylin and eosin, mag. 22.)

Of course, not every electrocardiogram of this type would be expected to reflect such peculiar location of the infarct, since there are several other factors which may account for the absence of the S-T elevation in the early stage of infarction. Thus, the acute S-T stage may be so transitory as to disappear before a record is taken. In other cases, the S-T elevation may be confined to the chest leads, with no evidence in the limb leads. One of the causes for this last is the coëxistence of tendencies influencing the position of the S-T segment in opposite directions such as occurs especially in cases with left ventricular preponderance and anterior wall

infarction, or in infarction of the mixed anterior and posterior wall type.

Only after these factors have been excluded may a limb plus chest lead electrocardiogram without S-T elevation early in acute myocardial infarction be considered possibly to reflect infarction not extending to the epicardium.

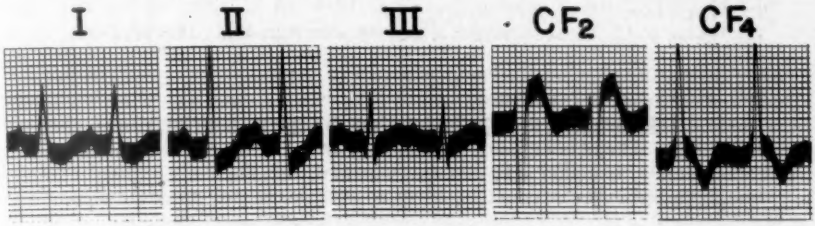

FIG. 3.—Five lead electrocardiogram of patient mentioned in addendum, taken 24 hours after the clinical attack and 24 hours before death.

Cases of recent myocardial infarction have been reported[9] with delayed changes in the electrocardiogram. In most of these instances, if not in all, characteristic T-wave changes developed long after the clinical diagnosis was made while the S-T elevation, the early electrocardiographic sign of infarction, was missing in the first so-called "negative" records. It would appear from the evidence in our case with postmortem control, that some of these cases of myocardial infarction with delayed electrocardiographic signs may also be cases with the same peculiar location of the lesion in the myocardium leaving the subepicardial layers uninvolved.

Summary. 1. A case is reported with recent myocardial infarction, proven at autopsy, in which elevation of the S-T segment was absent in the electrocardiogram taken during the acute stage. The absence of involvement of the subepicardial myocardium over the infarcted area is considered as the possible cause for the atypical record.

2. Cases of recent myocardial infarction with delayed electrocardiographic signs also may represent such cases of infarction of the subendocardial layers without involvement of the subepicardial layers of the myocardium.

3. Other causes for absence of this electrocardiographic sign must be excluded before this interpretation is entertained.

We are grateful to Dr. D. H. Levinthal for permission to report this case. We are indebted to Dr. O. Saphir for checking the anatomic findings and to Dr. L. N. Katz for his suggestions and aid in preparing this article.

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ANEURYSM OF THE CORONARY ARTERY.

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Aneurysms of the coronary arteries are rare. This is clearly indicated by the fact that Packard and Wechsler[9] in a review of the literature from 1812 to 1929 were able to find only 30 indisputable cases including one of their own. Twelve of the aneurysms were classified as arteriosclerotic, 7 as mycotic embolic, and 1 as pure mycotic in origin. Syphilitic aortitis was associated with 3 of the aneurysms of arteriosclerotic type, but it was believed not to have been an important factor in their development. In the remaining cases, the aneurysms could not be classified as to etiology.

The writer has been able to find reports of only 15 additional cases in the literature since Packard and Wechsler's survey in 1929. In 3 of these cases[2,5,10] the aneurysm belonged to the arteriosclerotic group. Vogelsang[13] cited a case in which aneurysm of the coronary artery was associated with gummatous myocarditis. In a remarkable case reported by Snyder and Hunter[12] a syphilitic aneurysm of the coronary artery was secondary to the burrowing of a syphilitic aneurysm of the sinus of Valsalva. Monahan[8] has also reported a case and cited one of Seydel's believed to be of syphilitic origin. Harris[7] collected 4 cases from the literature and added one of his own in which aneurysmal dilatation of the coronary artery was of congenital origin. Other coronary abnormalities that could perhaps be regarded as congenital aneurysms have been more properly considered in the literature under the heading of congenital anomalies of the coronary arteries. Rae[11] found aneurysmal dilatation of both coronary arteries in a case of rheumatic carditis. The coronary arteries were involved by an exudative, necrotizing inflammatory process suggesting that the aneurysms were also of rheumatic etiology. However, the possibility that the inflammatory reaction had been superimposed on a congenital lesion was pointed out. Abbott and Chase[1] have reported from this institution an additional case of mycotic embolic aneurysm of the coronary artery. De Navasquez,[3]

in a study of embolic myocarditis, cited one more case in which a mycotic embolic aneurysm of a coronary artery had occurred.

Of the 45 cases of aneurysm of the coronary arteries cited above, 35 were classifiable according to etiology. Fifteen of these were arteriosclerotic; 4 were syphilitic; 5 were of congenital origin; 1 was rheumatic; 9 were mycotic embolic, and 1 was pure mycotic. The case presented here is an additional example of aneurysm of the coronary artery of the mycotic embolic variety.

Case Report. The patient, a 45-year-old white male, a physician, was admitted to the Royal Victoria Hospital, Montreal, on August 8, 1939. Twenty years previously a diagnosis of rheumatic endocarditis had been made. Since that time he had led a cautious life and had not had any serious illnesses. Four months before admission to hospital, he had experienced chills and fever which, together with other symptoms and signs, had led to a diagnosis of subacute bacterial endocarditis. After admission to hospital this diagnosis was confirmed by the additional finding of *Strep. viridans* in blood cultures. Large quantities of sulfanilamide, sulfapyridine and heparin were administered but there was no improvement. After a severe constricting pain in the chest, on Sept. 20, he failed rapidly. Nevertheless, his death on Oct. 2, 1939 was unexpected, occurring as he was being propped up on a bed pan.

Autopsy (7 hours after death). The *heart* was enlarged (660 gm.) due largely to hypertrophy of the left ventricle. On the mitral valve were several large polypoid vegetations which extended along the chordæ tendineæ, some of which were ruptured. The valve itself was relatively thin and showed little evidence of antecedent endocarditis. The aortic orifice, however, was markedly stenosed, its lumen reduced to a stellate opening not more than 1 cm. in greatest diameter. The aortic valve cusps were fused, thickened, nodular and extensively calcified. The appearance was typical of healed rheumatic endocarditis. Along their free edges were soft, friable vegetations which, though smaller, were similar to those on the mitral valve. In the *anterior ramus descendens of the left coronary artery*, 2 cm. from its origin there was a saccular aneurysmal dilatation measuring 1.9 cm. in length and 1.6 cm. in its greatest diameter. The aneurysm caused a prominent bulge on the external surface of the heart, but had not ruptured. Its lumen was partially filled with thrombus material. The lumen of the artery as it entered the aneurysm was patent but at the distal exit it was occluded by thrombus material. The *myocardium* of the anterior wall of the left ventricle and of the interventricular septum near the apex showed evidence of recent infarction, being softened and discolored by yellow and red mottling. Mural thrombi were found attached to the endocardial surface of the right ventricle near its apex and in the right auricular appendage, but not in the left ventricle.

The *left pulmonary artery* was found to be occluded by a large unattached embolus composed of thrombus material similar to that found on the walls of the right side of the heart. The *spleen* was soft and large, weighing 705 gm.; it contained several large irregular infarcts of recent origin. Several smaller recent infarcts were found in the *kidneys* and there were small areas of infarction in the *mesentery* and *wall of the ileum*. In addition to these findings there was generalized arteriosclerosis of moderate degree, bilateral hydrothorax and chronic passive hyperemia of the lungs, liver and kidneys.

Histology. The mitral and aortic valves showed fibrous thickening which was slight in the former but marked in the latter. The vegetations were composed of masses of platelets with some fibrin and numerous colonies of Gram-positive cocci. Although the bacteria came close to the surfaces of the

vegetations they were almost everywhere separated from the surface by a thin layer of thrombus material. There was nothing in either the gross or microscopic appearance of the vegetations to suggest that they were different from those seen in cases of subacute bacterial endocarditis not treated with heparin. The coronary aneurysm was examined in serial sections (Fig. 1). A small segment of the circumference of the arterial wall next to the myocardium was still intact and recognizable, but the segment nearest the epicardium had been almost totally destroyed and was represented only by attenuated strands of partly necrotic muscle and elastic tissue which were stretched out to form a thin, delicate wall around the external aspect of the aneurysmal sac where it bulged into the epicardial fat. The lumen of the aneurysm was lined by a thin layer of thrombus, but it was in open communication with the lumen of the proximal segment of the coronary artery. The pericardial adipose tissue in the immediate neighborhood of the aneurysm was edematous, infiltrated by neutrophils and contained a few proliferating fibroblasts, while the pericardial surface over the bulging aneurysm was covered by a thin layer of fibrinous exudate. Special stains to demonstrate bacteria revealed many Gram-positive cocci in the aneurysmal wall, in the thrombus lining it and in the leukocytes around it. Sections of myocardium from the soft and discolored area of infarction showed necrosis of the heart muscle which was infiltrated in patchy fashion by considerable numbers of neutrophils. At the margins of the necrotic areas, beginning fibroblastic proliferation was apparent. Histologic sections of other organs and tissues confirmed the gross pathologic diagnoses.

Case Summary. A *Strep. viridans* infection of the mitral and aortic valve cusps, previously injured by rheumatic endocarditis, was the source of infected emboli which had caused multiple infarction of the spleen, kidneys, mesentery and ileum. One such embolus, lodging in the anterior descending ramus of the left coronary artery, had caused the development of a mycotic aneurysm at this site, while occlusion of the artery had led to infarction of the myocardium at the apex of the left ventricle. Mural thrombi in the right side of the heart formed the probable source of emboli which had occluded the left pulmonary artery. Pulmonary embolism was regarded as the immediate cause of death.

Comment. All of the 9 instances of mycotic embolic aneurysm of the coronary artery cited above, as well as the one reported here, have been associated with either vegetative or ulcerative bacterial endocarditis. In 9 of the 10 cases in which the information is available, the aortic and mitral valves were involved as follows: aortic valve alone in 4 cases; aortic and mitral valves in 4 cases; mitral valve alone in 1 case. Among 8 cases in which sex was given, 5 were males and 3 were females. The ages ranged from 22 to 45 years with an average of 31. In one of the cases[9] there were multiple aneurysms, one of the left and two of the right coronary artery. In 8 of the remaining cases there was a single aneurysm, involving the left coronary artery in 5 cases and the right coronary artery in 3. In only 2 instances was the position of an aneurysm of the left coronary artery specified; in 1 case the aneurysm was of the anterior ramus descendens and in the other of the circumflex branch. The sizes of the aneurysms ranged from 5 mm. in diameter to the

"size of a walnut." Among 8 cases in which the cause of death was indicated, it was attributed to coronary occlusion and myocardial infarction with its sequelæ in 3 cases, including the one reported here. In 2 cases sudden death was due to rupture of the aneurysm into the pericardial sac. In 2 cases death was attributed to "mitral heart failure," and in 1 case to uremia.

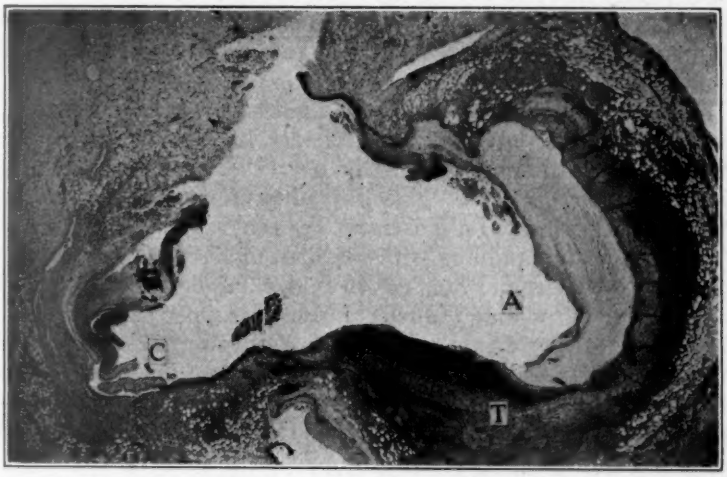

FIG. 1.—Photomicrograph (low magnification) of a transverse section of the anterior descending branch of the left coronary artery at the level of the aneurysmal dilatation. *C*, original lumen of the coronary artery with intact arterial wall at the left; *A*, lumen of aneurysmal sac; *T*, laminated thrombus lining the extremely thin-walled aneurysm.

The formation of mycotic embolic aneurysm of the coronary artery depends upon the lodgment of an infected embolus in the lumen of the artery. That such aneurysms are rare is due in part to the rarity of gross coronary embolism and in part to the fact that such large emboli may cause death from coronary occlusion before sufficient time has elapsed for the development of mycotic aneurysm. Although microscopic embolism of the small coronary branches is common in bacterial endocarditis, the bacteria contained in these minute emboli are rapidly phagocytized as de Navasquez has shown.[3]

The rarity of gross coronary embolism, has been variously attributed[4,5] to the difference between the caliber of the aorta and that of the coronary orifices, to the situation of the coronary orifices in the sinuses of Valsalva, to the right angle of emergence of the coronary arteries, to the bulk and swiftness of the blood current in the root of the aorta and to the fact that the major part of coronary filling occurs during diastole. However, since it has been shown[3] that minute emboli frequently enter the coronary arteries, it is clear

that the size of emboli large enough to occlude the main coronary branches must be the factor determining the rarity of gross coronary embolism. Emboli of sufficient size are probably not nearly as numerous in bacterial endocarditis as are minute emboli. If a great many emboli of microscopic proportions are released into the blood stream and thoroughly mixed, then it is obvious that the number of these emboli entering the coronary arteries will be in proportion to the coronary blood flow. On the other hand, larger emboli of exactly the correct size to occlude one of the coronary arteries or its main branches will much less frequently be released from the endocardial vegetations.

When an embolus of exactly the right size is released it will, by reason of its size, have greater difficulty in entering the coronary arteries, for its dimensions must be nearly as great as the diameter of the coronary orifices. The difficulty of its entrance into the coronary orifices may be illustrated by analogy with a device used by small boys in gambling with marbles. This device consists of a cigar box with a round hole cut in its lid, large enough to admit a marble freely, providing that the marble is dropped straight through the hole. However, unless the aim is accurate, the marble strikes the edge of the hole, bounces away and does not enter the box. In the same way, an embolus only a little smaller than the coronary orifices probably does not enter unless it is carried directly into the orifice without being deflected by impact with its margins.

Summary. A case of mycotic embolic aneurysm of the anterior descending branch of the left coronary artery is presented. A review of the literature reveals 45 cases of coronary aneurysm and 9 of aneurysm of mycotic embolic origin. In this instance, the source of embolism was a vegetative endocarditis of mitral and aortic valves due to the *Strep. viridans*. Impaction of the infected embolus in the coronary lumen caused not only the development of aneurysm but also coronary occlusion with infarction of the myocardium. The reasons for the rarity of mycotic embolic aneurysms of the coronary arteries are briefly discussed.

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A NOTE ON THE DEVELOPMENT OF CUTANEOUS ARTERIAL "SPIDERS" AND PALMAR ERYTHEMA IN PERSONS WITH LIVER DISEASE AND THEIR DEVELOPMENT FOLLOWING THE ADMINISTRATION OF ESTROGENS.

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In the course of a clinical study of the acquired cutaneous arterial "spider" found in subjects with liver disease, pregnancy and nutritional deficiency disorders, during the past several years observations have been made on 359 persons with these curious stigmata. Some 250 have been followed for periods varying from several days to 5 years. Certain other vascular phenomena have been noted under similar circumstances, particularly the palmar erythema, vascularization of the skin of the nose, engorgement of the nasal mucosa, vascular dilatations in the conjunctiva and the mucous membrane of the mouth. The data accumulated are now being prepared for publication.

On the basis of these observations, and from a study of various reports which have come to my attention, the idea occurred that these vascular alterations might be related to an abnormality in the metabolism of certain 17-ketosteroid hormones, particularly the estrogenic substances. It is generally agreed that estrogens are inactivated, changed or destroyed in the liver as has been shown in heart-lung-liver preparations by Israel, Meranze and Johnson.[1] Furthermore, alterations in 17-ketosteroid metabolism have been reported in persons with cirrhosis of the liver by Edmondson, Glass and Soll,[2] who found abnormal estrogen and androgen excretion in several instances of gynecomastia. The well-known increase in excretion of estrogenic substances in pregnancy coincides with the period during which vascular spiders and palmar erythema tend to appear.[3] The acute action of estrogens upon the minute vessels in the ear of ovariectomized rabbits has been reported by Reynolds and Foster[4] to cause dilatation. It is not unlikely that a protracted action might affect blood-vessels throughout the body as well as those of the female genital tract which have been investigated extensively. In this connection the studies of Bartelmez and Markee on the spiral arteries in the endometrium at least suggests a morphologic similarity to the cutaneous arterial spider which we have found to be a small coiled end-artery in the subcutaneous tissue.[3] A study of a serially cut vascular "spider" indicates close similarity to the

endometrial end-artery pictured in a reconstruction by Jones and Brewer.[5] An additional suggestion presented itself when we found that during the menstrual cycle, there were visible changes in the arterial spider in the skin of certain normal women who had acquired them during pregnancy.

As collateral evidence of an important ketosteroid action in relation to function of the cutaneous circulation should be mentioned the work of Edwards, Hamilton, Duntley and Hubert[6] who found the skin of castrate and eunuchoid men to be very pale and to contain little hemoglobin and most of that in the reduced state. When the endocrine disorder was ameliorated or corrected by androgenic therapy there was a spectacular increase in the vascularity of the skin with a preponderant rise in the oxyhemoglobin. The skin of the hands and feet became distinctly red.

It was therefore decided to administer estrogenic materials to certain persons with presumptive or diagnostic evidence of liver disease. Diethylstilbestrol and alpha-estradiol-dipropionate* were used. As controls, elderly white males with coronary artery disease were treated similarly, but showed no changes in the skin.

Three white males who had been addicted to alcohol for many years were treated.

The first, a 49-year-old man had been observed to have characteristic palmar erythema during the course of a left upper and lower lobe pneumonia (Type I pneumococcus) which in turn had complicated delirium tremens. Following sulfapyrazine therapy recovery occurred and the color of the palms returned to normal. For 2 weeks after discharge he was given 2 mg. of diethylstilbestrol by mouth every day and examined at intervals. No change occurred in the palms, the only symptoms were slight pain in the testicles and engorgement of the nasal mucosa.

The second subject, a 60-year-old man, had been admitted to the hospital for a right upper lobe pneumonia (Type II pneumococcus) which occurred after a bout of drunkenness. He was found to have several typical vascular "spiders." He responded to sulfathiazole therapy and when afebrile was started on 2 mg. of diethylstilbestrol by mouth which was continued for 17 days. On the fifth day of this treatment he was given an intramuscular injection of 0.4 mg. of alpha-estradiol dipropionate and this was repeated daily from the eighth through the seventeenth day. On the tenth day after institution of diethylstilbestrol therapy it was noted that the size of his vascular "spiders" had increased, and that they were redder than before. Two days later several new spots appeared and 3 days after this definite radicles could be seen branching from the central red punctum. After treatment had continued for 17 days he went home. When seen 9 days later all of the "spiders" had faded, and 2 of the newly acquired ones had disappeared.

The third subject, a 44-year-old man had cirrhosis, with jaundice, ascites, a red nose with prominent vessels and several characteristic arterial "spiders," one of which pulsated palpably. Six weeks after admission, when the jaundice and ascites had disappeared, he was given 0.2 mg. of alpha-estradiol dipropionate intramuscularly on alternate day for 5 doses. After the third injection his nose became much redder and the vessels more promi-

* The latter was supplied by the Ciba Pharmaceutical Products, Inc.

nent. He was then discharged and given 2 mg. of diethylstilbestrol daily. At the end of 2 weeks it was found that he had acquired 2 new cutaneous "spiders" and those previously noted had increased in size and prominence. By the end of the fourth week his nose was livid and the vessels were very prominent. In both palms the characteristic findings of palmar erythema, most noticeable in the ulnar pad, had appeared. This finding had not been present before. In the proximal part of the right ulnar pad a typical vascular spider had developed though they are very rare in the palm. The medication was discontinued and 2 weeks later the palms were almost normal in color except for a faint red punctum which marked the site of the vascular "spider." Several of the other spiders had faded and the nose was more nearly normal in appearance. No studies were done on the urinary ketosteroid excretion. There was no clinical suggestion that the liver functions were declining during the period in which the vascular phenomena appeared.

Discussion. The events following estrogen administration to the second and third subjects suggest that the occurrence of vascular "spiders," and palmar erythema may be related to the state characterized by an imbalance or upset in metabolism of the 17-ketosteroids. Whether this be a result of estrogenic substances acting directly upon skin vessels, or is a result of a hormonal imbalance in which androgens appear in large amounts to counteract the administered estrogens, or whether the pituitary is involved remains purely speculative. It is not certain that concurrent liver function failure did not occur, or that the compounds given did not interfere with some liver function. These possibilities remain to be investigated. No doubt other interpretations will occur to those well-versed in the perplexing literature on endocrine metabolism. These preliminary studies, along with much unpublished material on aberrant endocrine and sexual manifestations in chronic liver disease suggest that a careful study of hormonal equilibrium in liver disease should be made.

The data reported in this note are brought forward in this present incomplete state because an opportunity to continue these observations in the near future now seems remote.

Conclusion. The development of cutaneous arterial "spiders" in 2 of 3 chronic alcohol addicts and palmar erythema in 1, following therapy with potent estrogens suggests that these stigmata of liver disease, pregnancy and deficiency diseases may result from abnormal metabolism of the 17-ketosteroid hormones.

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THE PROLONGED EFFECT OF AMPHETAMINE SULPHATE IN GELATIN.*

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When an aqueous solution of amphetamine sulphate is introduced parenterally, its effects wear off within a few hours. On the other hand, the elimination of the amine outlasts its physiologic effect by many hours (Richter[4] and Beyer and Skinner[1]). In the present study, an attempt was made to prolong the effects of the drug by delaying its absorption. The vehicle used for this purpose was gelatin, which was selected for the following reasons: 1, its liquefied state is readily maintained; 2, it does not irritate the tissues; 3, it produces no antigen reactions as do other proteins (Wells,[7] Hooker and Boyd,[2] and Kahn and McNeil[3]); 4, amphetamine sulphate is a stable, water-soluble substance which is freely miscible in gelatin.

Gelatin has been previously used to prolong the effects of other water-soluble drugs such as insulin and epinephrine.

Successful results with a gelatin-epinephrine mixture have been reported by Spain, Strauss and Fuchs,[6] who used it in the treatment of allergic conditions, such as chronic bronchial asthma. These authors reported a sharp reduction in the number of doses of epinephrine required daily when this preparation was substituted for the aqueous solution.

Procedure. The effects of amphetamine sulphate in aqueous and gelatin were compared: I On the circulatory system of man; II On the gastro-intestinal tract; 1, by Roentgen-ray studies in man; 2, by their effects on the absorption of ethyl alcohol in man, (the subjects of these studies were passive schizophrenics, with the exception of one chronic alcoholic with the residuals of Korsakoff's psychosis); 3, by direct observation of the gastro-intestinal tract in guinea pigs.

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I. *Effect on the Blood Pressure and Pulse Rate in Man.* The subjects received intramuscular or subcutaneous injections of the amphetamine-gelatin solution in doses varying from 20 to 50 mg. The blood pressure and pulse rate were followed for several hours, in some instances as long as 120 hours. The following week the subjects received the same dose of the drug in the aqueous solution. It was found that the effects of the injections of the amphetamine-gelatin mixture did not differ significantly from those of the aqueous solution, that is, the onset and the duration of the rise in blood pressure were practically equal following the administration of

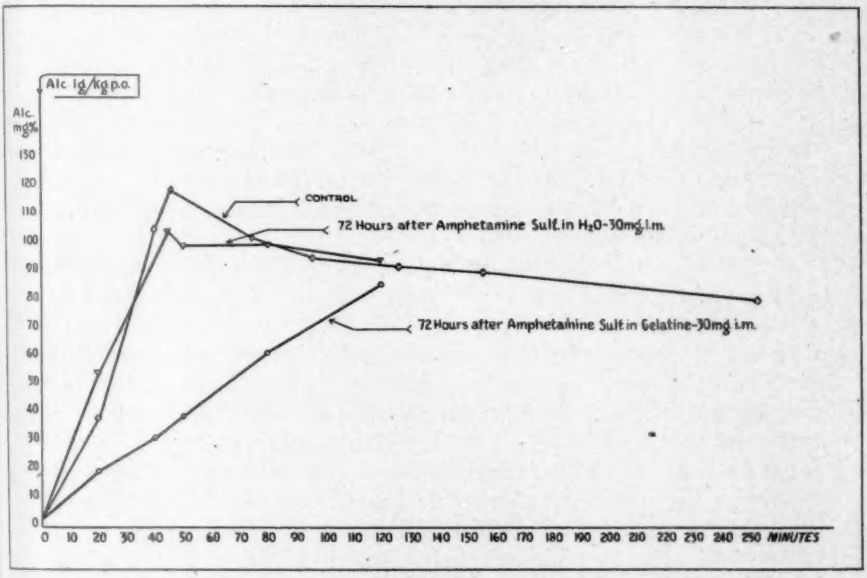

CHART 1. Prolonged effect of amphetamine sulphate in gelatin.

the amphetamine-gelatin mixture than following the aqueous solution of the drug. Equivalent decreases in the pulse rate also occurred.

II. *Effects on the Gastro-intestinal Tract.* The majority of authors agree that amphetamine sulphate in aqueous solution produces the following effects: the tonus of the stomach and intestines are decreased. This is in association with a marked dilatation and a decrease or abolition of the peristaltic movements of the stomach and colon. These changes appear to be less marked in the small intestines.

Recent investigations (Rinkel and Myerson[5]) have demonstrated another effect of amphetamine sulphate on the gastro-intestinal tract; namely, a marked delay in the absorption of ethyl alcohol.

This delay is in part due to prolonged emptying time of the stomach, and in part due to alteration of the absorptive mechanism of the small intestine which was demonstrated following direct introduction of ethyl alcohol into the duodenum.

1. *Roentgen Ray Studies in Man.* The subjects of these studies had no demonstrable disease of the gastro-intestinal tract. They were given an opaque meal (consisting of 4 ounces of barium sulphate, thoroughly stirred in 6 ounces of water), routinely used in Roentgen studies of the gastro-intestinal tract. A fasting period of 14 hours, during which no food or liquids were ingested, preceded the Roentgen ray examination. Films of the stomach with the patient lying prone, were taken at intervals of 1, 2, 3, 6 and 48 hours. In one patient, the examination was extended so that additional films were taken at 96 and 120 hours. In two instances, Roentgen rays of the colon were taken following a barium enema, 4 hours after the administration of amphetamine sulphate.

a. Effect on the Emptying Time of the Stomach. Both preparations delayed the emptying time of the stomach. The gelatinous mixture, however, produced a greater delay in this function than did the aqueous solution, the comparative emptying times being 3 to 6 hours and 2 to 3 hours respectively.

b. Effect on the Tone of the Colon. Both the aqueous and the gelatinous preparations of amphetamine sulphate produced atonicity of the colon which was characterized by shallow contractions and a decrease in number or practically complete absence of haustrations. In 2 cases, however, a marked contrast in the effects of the two preparations was apparent. In the first case, following the administration of the amphetamine-gelatin mixture, marked atonicity of the colon developed which was present even after 120 hours had elapsed. Following the administration of the aqueous solution in this subject, only slight atonicity, which lasted for 72 hours, was apparent. In the second case, in which a spastic colon did not respond to the administration of an aqueous solution of amphetamine, relaxation and atonicity were produced by administration of the gelatinous solution. These changes lasted for at least 48 hours.

2. *Absorption of Ethyl Alcohol.* In these experiments, the aqueous and gelatinous preparations of the drug were administered to fasting subjects who were then given by mouth 1 gm. of ethyl alcohol per kilo body weight. The blood alcohol level was determined at intervals up to 250 minutes after the ingestion of the alcohol. The diagram illustrates the curve of alcohol absorption in a subject at the 72-hour interval. The chart demonstrates: 1, normal alcohol absorption as a control; 2, the great inhibition of alcohol uptake 72 hours after the intramuscular injection of 30 mg. of amphetamine-gelatin mixture; 3, the return to normal of the alcohol uptake 72 hours following the intramuscular injection of aqueous amphetamine sulphate.

3. *Direct Observation of the Gastro-intestinal Tract in Animals.* Twenty-eight guinea pigs were used in these experiments. Direct exposure of the gastro-intestinal tract was carried out under local anesthesia. These animals are very responsive to amphetamine sulphate and yet tolerate the drug in doses as high as 10 mg. per kilo body weight. If the dosage is further increased, the animals die after developing convulsions. The animals were divided into 4 groups:

1. Control (6 animals),

2. Receiving intramuscular injections of amphetamine sulphate in aqueous solution (4 animals).

3. Receiving intramuscular injections of the amphetamine-gelatin mixture (14 animals). Of this group, 3 animals were examined in 24 hours; 6 in 48 hours; 4 in 72 hours, and 1 in 120 hours.

3. Given epinephrine in gelatin (4 animals). One is impressed, on exposing the abdominal cavity of the animals that received the amphetamine-gelatin mixture, by the "calmness" of the gastro-intestinal tract. Only occasionally is a peristaltic wave of the small intestine observed. The stomach and colon are markedly distended, relaxed and practically without tone. The small intestine shares these latter changes, but to a lesser degree. The color of the whole tract is grayish-white as though the blood were greatly diminished in quantity. In most cases, the gall-bladder is also greatly distended. The duration of these effects is at least 72 hours following a single injection of amphetamine-gelatin mixture, and it is only after an interval of 120 hours that the gastro-intestinal tract is restored to its normal state. Although similar changes were noted in the animals who received the aqueous preparation of amphetamine sulphate, they lasted for only 1 to 2 hours. In the control group, none of the above changes were noted. In the animals that received epinephrine in gelatin, none of the changes observed following the administration of amphetamine were noted 24 hours after administration of the drug.

Summary. The following comparative effects of amphetamine-gelatin mixture and aqueous amphetamine solution were observed:

1. Circulatory System: The increase in blood pressure and the corresponding decrease in pulse rate produced by amphetamine was not delayed or prolonged when the drug was dissolved in gelatin.

2. Gastro-intestinal System: There was a definite prolongation of the characteristic effects of amphetamine sulphate (decrease in tone and peristalsis) when the drug was mixed with gelatin. This action was observed in man following Roentgen ray studies, and in animals by direct observation of the gastro-intestinal tract.

3. The delay in absorption of alcohol which follows the administration of amphetamine sulphate is definitely more marked when the drug is mixed with gelatin.

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THE TREATMENT OF UNDERWEIGHT WITH INSULIN.

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Since Pitfield[13] observed a gain in the weight of children by the use of insulin, and the report of Falta[6] confirming in adults Pitfield's experiments, many clinical and experimental papers have appeared in the literature dealing with the use of insulin in non-diabetic malnourished patients and the mechanism by which this hormone acts.[1–3,7,9–11,15]

Though there are many contradictory opinions regarding the mechanism of action of insulin in bringing about a gain in weight, it seems that the more accepted explanation is that insulin, by vagal action,[14,16] produces hypermotility of stomach and hunger sensation, this action being enhanced by the hypoglycemia which results.[5] Besides, as observed by Okada *et al.*[12] and by Lueders and Watson,[8] insulin in sufficient amounts brings about an increase in the amount of gastric and biliary secretion, and consequently a better digestion and assimilation of the food.

Plan of Treatment. Our plan of treatment, based on physiologic and experimental grounds, is original so far as we know. Insulin is injected only onee a day in order to avoid a compensatory inhibition of the internal secretion of the pancreas for lack of natural stimulus by way of alimentation. Insulin, if injected before every meal, would take care of the postprandial hyperglycemia, leaving the pancreas without action. As Clark, Gibson and Paul[4] observed, there is lowered tolerance for glucose in individuals taking insulin, evidently because of lack of stimulus to the endocrine function of the pancreas.

The dosage of insulin we employ is progressive, beginning with 8 units and increasing according to the patient's appetite on the previous day, but we never have exceeded 30 units, except in Case 12 by his own mistake.

The time of injection is about 45 minutes before the noon meal. In Brazil, where this experiment was conducted, we take 2 large meals a day—one about midday and the other about 6 P.M. We advise the patients to eat when they begin to feel hungry, because the hunger reaction of insulin does not appear exactly within 45 minutes, but is subject to variation in different patients.

When the desired effect is attained with a sufficient gain in weight, we begin to discontinue the administration of insulin, not abruptly but gradually, injecting the hormone in the inverse dosage of the beginning of treatment, that is to say, if we began by injecting 8, then 10, 14, 20 units, we discontinue by giving 20, then 14, 10, 8 units, then it is completely discontinued. In this way the stimulus to the pancreas is gradually restored, so that if this gland has been spared during the treatment it regains its function progressively. The administration of insulin* only once a day and its gradual discontinuance protects the endocrine function of the pancreas. We have had no case of glycosuria in our patients after finishing the treatment.

We think it is dangerous to inject insulin more than once a day because of the possibility of inhibition of the islets of Langerhans. In cases with diabetic history in the family it is advisable to subject the patients to a glucose tolerance test to assure the possibility of instituting treatment without inconvenient results.

Results. All cases gained weight, this gain varying from 1 to 27 pounds (average 8.7) (Table 1).

The appetite increased considerably, as well as the palatability of the food. The unanimous statement of the patients was that they ate considerably more than formerly; to quote their expression, "as never before in their life."

Most of them observed also that the treatment had a euphoric effect. It should be pointed out, however, that the esthetic satisfaction of gaining in weight may have some influence in this feeling.

All our 30 cases were healthy persons with no other complaint except underweight and lack of appetite. Their underweight was of long standing. Their age varied from 17 to 50 years; 22 were male and 8 female.

Is the Action of Insulin a Psychic One? During the prosecution of this study we had opportunity to investigate the opinion of Freyberg[7] that the effect of the pancreatic hormone is exercised through psychic action.

We changed the contents of insulin vials to which the patients were familiarized for sterilized physiologic solution, and acted in the

* The insulin employed in all our cases was either Lilly or Schering.

same way as though it were insulin—perforated the rubber cap, simulated to ascertain the number of units and injected this placebo. All patients subjected to this experiment complained, on the following day, of lack of appetite after the injection. When we returned to real insulin their appetite again improved. We made this observation in the middle of the treatment when the patients had already experienced an improvement in appetite. The placebo was therefore tried during 4 or 5 days in the middle of the treatment without the patient's noticing that we had changed the contents of the insulin vials. We are certain that the effect was not due to suggestion, for when we gave insulin again the patient himself informed us that something had gone wrong in the previous days in which he was getting a placebo without knowing it.

TABLE 1.—GAIN IN WEIGHT OF THE INSULIN TREATMENT.

Cases.	Patients.	Sex.	Age (yrs.).	Weight before treatment (pounds).	Units (av.).	Days of treatment.	Weight after treatment.	Gain in weight.
1	F. J. B.	M	50	101	17	20	106	5
2	O. B. J.	M	34	133	20	15	139	6
3	L. C.	F	17	118	15	20	122	4
4	A. G. O.	M	31	121	21	15	128	7
5	J. B.	M	32	97	13	12	99	2
6	A. O. L.	M	29	134	23	60	154	20
7	J. B. G.	M	29	110	20	40	121	11
8	G. M.	M	34	124	24	40	133	9
9	L. B. G.	M	32	121	20	42	134	13
10	L. M. F.	F	24	93	15	20	94	1
11	C. M. M.	F	26	95	16	30	102	7
12	M. P. B.	M	32	94	34	45	121	27
13	A. G. F.	M	35	134	20	34	149	15
14	E. C.	F	30	95	15	30	102	7
15	R. N.	M	36	105	20	45	117	12
16	J. D. A.	M	38	97	15	15	100	3
17	J. L. C.	M	24	124	20	30	131	7
18	G. V.	M	27	120	20	30	132	12
19	F. F.	M	37	101	20	30	104	3
20	J. M.	M	25	98	20	30	106	8
21	M. S.	F	25	89	19	30	98	9
22	M. R.	M	38	126	18	30	132	6
23	A. J. F.	M	23	106	20	36	118	12
24	J. C. V.	M	22	128	20	35	142	14
25	A. J. G.	M	24	119	20	15	123	4
26	V. P.	M	29	130	20	30	138	8
27	J. A. L.	M	33	103	20	34	112	9
28	L. F.	F	30	94	20	31	101	7
29	L. R.	F	34	96	16	27	101	5
30	R. V.	F	20	90	20	30	100	10
Average				109.8	19.3	30	118	8.7

Summary. 1. We have briefly reviewed the literature dealing with the use of insulin in the treatment of underweight.

2. A new plan of treatment is outlined in which the patient receives insulin only once a day in progressive doses and finishes by receiving the hormone in the inverse dosage of the beginning of his treatment.

3. The possibility of inhibition of the internal secretion of the pancreas when insulin is given several times a day is discussed.

4. The opinion that the effect of insulin in underweight is psychic is also discussed and refuted.

5. All the 30 cases submitted to treatment gained weight, from 1 to 27 pounds (average 8.7).

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THE INHERITANCE OF DIABETES INSIPIDUS.*

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There are a number of causes of diabetes insipidus such as brain tumor, trauma, Christian's syndrome (multiple xanthomatosis), syphilis, encephalitis, other infections and idiopathy. However, heredity is not regarded ordinarily as a cause of diabetes insipidus. Nevertheless, in reviewing the literature, there are reports which show that diabetes insipidus may be inherited and transmitted through many generations of a family. Probably, the reason inheritance has not been given much attention here is that nearly all the references on this subject are in the foreign literature.

I have observed for 5 years a boy with diabetes insipidus whose mother and grandmother had the disease. It appeared of value to present their cases and to give a review of the literature.

One of the most interesting and illuminating reports on the inherited tendencies or the familial characteristics of diabetes insipidus is that given by Weil[32] and his son.[33] In 1884, when Adolph Weil[32]

* The term "diabetes insipidus" means a marked polyuria and polydipsia which usually ranges from at least 6 to 10 liters a day and is relieved by pituitrin. The polyuria and polydipsia are even present during the night when the patient is in bed.

was professor in Heidelberg, he studied four generations of a family of 91 members headed by a man with diabetes insipidus and found that 24 of these had the disease. Later in 1908, his son Alfred Weil[33] continued his father's studies and found that in five generations of this family there were 35 cases of diabetes insipidus among 220 members. Two-thirds of the cases were men and one-third were women. A number of these patients lived to very old age. For example, 2 daughters who had the disease their whole life were 87 and 92 years old. The inheritance of diabetes insipidus has been known as far back as 1841 when Lacombe[16] reported its occurrence in 5 males and 3 females in two generations of a family. Trousseau,[30] too, suggested it, and later Lanceraux[17] commented on the familial tendencies of the disease in several patients.

Certain accounts by authors on the number of persons affected with diabetes insipidus in various generations of individual families may be briefly presented as follows: Deebrey,[6] 5 cases in two generations; Wachsmuth,[31] 2 cases in one generation; Reith,[27] 5 cases in two generations; Gee,[11] 11 cases in four generations; Pain,[26] 7 cases in three generations; Orsi,[25] 6 cases in two generations; Clay,[5] 3 cases in one generation; Lauritzen,[19] 9 cases in four generations; Sasse,[29] 8 cases in three generations; Marinesco,[23] 3 cases in two generations; Knopfelmacher,[15] 5 cases in four generations; Ehrmann,[7] 3 cases in one generation; Marañon and Bonilla,[22] 2 cases in two generations; Lange,[18] 4 cases in two generations.

Other extraordinary observations on this phase of the disease have been made by McIlraith[21] who presented 3 familial cases, 2 of which were brothers. The third case was a boy whose 3 brothers, mother, maternal grandmother and an aunt were all affected. Chase[3] traced diabetes insipidus through five generations of a family which appeared remarkable in that in the fourth generation as many as 10 out of 23 children had the malady. Chester and Spiegel[4] studied the family of a woman with polyuria whose father, paternal grandmother, maternal grandmother and a maternal aunt were similarly afflicted. Curiously, 1 child of the woman's first marriage and 1 of the second marriage had diabetes insipidus. Gänsslen and Fritz[10] saw a patient with an ulcer of the stomach and diabetes insipidus who gave the history that he as well as his only son had the disease since early youth and that no amount of scolding or beating by the patient's parents could make him stop drinking water. In addition, they studied the tree of a very large family by delving into the records of births, deaths and marriages for seven generations which went back to about 1700. They found that the disease was carried through the last five generations with members with the disease in each of these. Levit and Pessikova[20] found 3 cases of familial origin out of their 16 cases of diabetes insipidus. A most interesting investigation was made more recently by Eller-

man[8] who was consulted in 1937 by a man, aged 23 years, with diabetes insipidus since childhood. The man explained that a brother, as well as his father and grandfather, also had this syndrome. Further inquiry revealed that this family had been studied by Lauritzen[19] in 1893 when it was discovered that 9 of 15 members had the disease. In 1938, this family had 73 members, of whom 26 (11 females and 15 males) were found to have polyuria. His records indicated that the majority of these patients had a daily diuresis of from 12 to 16 liters while in others it was less severe, amounting from 4 to 9 liters. He believed that the mode of hereditary diabetes insipidus seemed to be one of simple dominance.

Bulloch,[2] Just[13] and Hogben[12] discussed the inheritance of the disease from certain selected references in the literature without adding any of their own cases. Bulloch[2] presented some detailed outlines and charts of each family tree to which he referred. In addition, there have been other contributions to this study.[1,9,24,28] I have been unable to confirm some references on the subject or to tell the number of persons affected because of the manner in which the material was presented.

Report of a Family. *Son.* This patient is a 25-year-old, bright, single man of Scandinavian descent whom I have observed for approximately 5 years. His history aside from his diabetes insipidus is irrelevant. The family history is important because his mother and grandmother also had this clinical entity. Details of this will be given in connection with their cases. He has never had any brothers or sisters. His father died of heart disease at the age of 48 when the patient was 6 months old. The patient has had diabetes insipidus since infancy and was a bottle-fed baby. His mother noticed that just as soon as he could walk and reach for water, he drank all he could get and was always after it. As he grew older, he imbibed as much as 3 or 4 gallons of water a day. Most of our observations have shown that his daily fluid intake and output have been about 10 to 12 liters. Pituitrin administered intramuscularly or intranasally in sufficient amounts reduced the polyuria and polydipsia to normal.

The physical examination showed a well-developed and well-nourished young man with no abnormal findings. His height was 6 feet and his weight was 193 pounds.

A number of laboratory examinations have been made. Roentgen rays of the skull were normal. The Wassermann and Hinton tests were negative. The spinal fluid was normal. The basal metabolism was −7%. The blood findings were as follows:

	Without pituitrin	With pituitrin
Hemoglobin	90%	
RBC	4,740,000	
Hematocrit	39%	41%
Hematocrit, Plasma	61%	59%
Calcium	12.6 mg./100 cc.	
Phosphorus	4.3 mg./100 cc.	4 mg./100 cc.
Chloride	339 mg./100 cc.	357 mg./100 cc.
Cholesterol	294 mg./100 cc.	269 mg./100 cc.
Sugar	84 mg./100 cc.	72 mg./100 cc.
NPN	32 mg./100 cc.	34 mg./100 cc.
Serum protein	7.7 gm./100 cc.	6.5 gm./100 cc.

Mother. The patient's mother is a 51-year-old widow. She consumed much water since childhood and always took a quart or more to bed with her up to 10 years ago. At 41, about the time of her menopause, her diabetes insipidus improved and now she takes daily about 5 to 6 liters of fluids. Except for the polyuria and the polydipsia she has always been quite healthy. She had no difficulty with the pregnancy or with the birth of her son, her only child. She had 1 brother who died of tuberculosis at the age of 24. Another brother died in infancy of unknown cause. She had no sisters. Her father is 75 years old and quite well.

Her general physical examination has been normal. Her height is 65½ inches and her weight 135 pounds.

Grandmother. The grandmother was a woman who drank more than 2 gallons of water a day when she was a girl. She, too, took a quart or more of it to bed with her until the age of 60. However, she improved at the age of 40, about the time of her menopause, but she still had polyuria and polydipsia at 64, when she died of chronic myocarditis and coronary disease. She had 4 brothers, 1 of whom died of diabetes mellitus. Her height was 63 inches and her weight was 165 pounds.

Comments. Study of the records of 70 patients in this clinic with diabetes insipidus due to various causes revealed only the case presented here with a story of familial diabetes insipidus, although the familial incidence of diabetes mellitus was comparatively common in these cases and in those presented in the literature.

Diabetes insipidus is a disease which may be inherited and transmitted through many generations of a family through the maternal or paternal side to either male or female children. When this disease is inherited, it may be found rather frequently in such a family. Inherited diabetes insipidus occurs ordinarily more often in males than females and sometimes skips a generation only to appear in the next. The birth of children with the disease to normal mothers, 1 of whose parents had diabetes insipidus, suggested to some authors that the transmission of polyuria at times simulated that of hemophilia.

Inherited diabetes insipidus may appear shortly after birth or later in life. For example, Klaften[14] reported a 24-year-old woman with diabetes insipidus for 21 years who gave birth to an apparently normal baby that at the age of 4 weeks already took more fluids than normal. On the other hand, the 2 brothers and sister of the family presented by Clay[5] all developed the disease at the age of 9 years. Polyuria is never present at birth.[4] Beginning with the age of about 2 years, the symptoms of hereditary diabetes insipidus are likely to appear.

There is a rather general impression that familial diabetes insipidus is due to a dominant gene. This view was based chiefly on the large family presented by Weil. Levit and Pessikova[20] believe there is questionable validity in drawing conclusions from select rather than comprehensive material gathered from the literature, as done

by Bulloch, because it creates the impression that practically every case of polyuria is a familial one. They concluded that the development of familial diabetes insipidus is due to a conditionally dominant gene showing poor penetrance. However, I believe that once diabetes insipidus has been shown to be inherited by a person, there is a good possibility that this individual may pass the disease on to some of his offspring.

Summary. This paper gives a review of the literature on familial diabetes insipidus and presents the cases of a boy, his mother and maternal grandmother, all of whom had diabetes insipidus.

Diabetes insipidus is a disease which may be inherited and transmitted through many generations of a family through the maternal or paternal side to either male or female children.

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INTRAMUSCULAR PRESSURE.

I. During Postoperative Depression.*

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It has been shown[4] that variations in intramuscular pressure occur in the period of postoperative depression, and in shock. Our observations confirm these changes in intramuscular pressure following surgical procedures.

Alterations in intramuscular pressure, or "muscle tonus" as Yandell Henderson prefers to term the phenomenon, may play an important rôle in shock and allied conditions.[3] The purpose of this study is to determine the nature of the intramuscular pressure changes during the natural course of the postoperative period in patients who recover without the appearance of complications after surgery.

Henderson devised an instrument, modified by Kerr and Scott,[5] with which intramuscular pressure could be directly measured. Experimental evidence indicates that Henderson's method for the measurement of intramuscular pressure is accurate.[2] The accumulated data of Henderson and his co-workers show values for the muscle at rest in normal individuals of from 60 to 90 mm. of water.[4] The pressure, in relaxed muscles, remains relatively constant from day to day.[2] We have found variations of from 5 to 10 mm. in the reading of the instrument, and variations on different days on the same individual within the error of reading the instrument, and occasionally an extreme of 15 mm. daily difference in the normal.

Certain factors are known to alter intramuscular pressure. Anesthesia decreases the pressure. Overventilation, the inhalation of carbon dioxide gas, the administration of strychnine, and stimulation of the skin by moving currents of air, will all increase intra-

* Read before the staff of the Cedars of Lebanon Hospital, Los Angeles, Calif., May 20, 1940.

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muscular pressure in *normal individuals*.[4] Henderson studied 7 patients after surgery and noted a fall in intramuscular pressure on isolated readings.[4] Other than his observations, there are no data on the entire postoperative period on patients following surgical procedures. Such data are presented in this study. Studies on intramuscular pressure, and on venous pressure in postoperative depression, shock, atelectasis, and in collapse following hemorrhage will be published in another communication.

Methods. Intramuscular pressure was measured, according to the method of Henderson in the biceps muscle.*

The apparatus can be easily constructed with the tools found in the average clinical laboratory (Chart 1). The method of obtaining readings

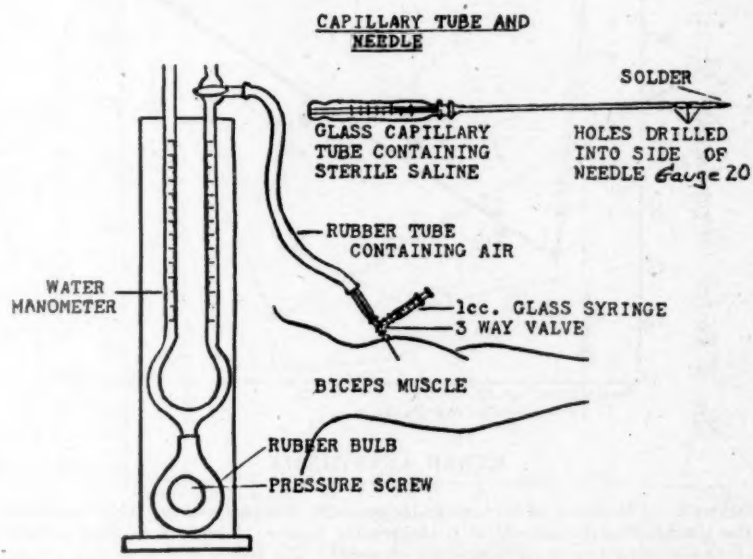


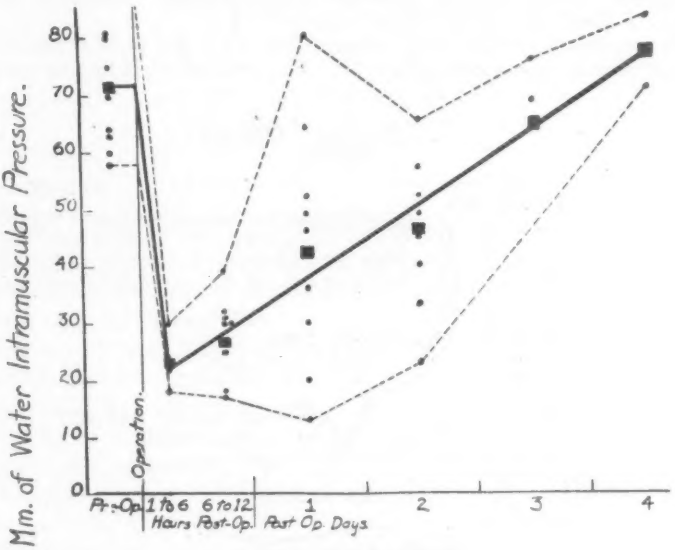
CHART 1.—The Henderson apparatus for the measurement of intramuscular pressure.

must be especially emphasized. It will be noted that the fluid in the capillary tube does not show a definite meniscus when the needle is first inserted into the muscle. As the pressure is increased by turning the thumbscrew, it will be noted that a meniscus appears with the convexity toward the muscle. The maximum curvature in the meniscus occurs when the pressure of the system is about equal to the intramuscular pressure. A slight increment of pressure within the system then starts movement of the fluid into

* The biceps muscle is easily accessible and does not have a tight fascial covering. Wells *et al.*[5] showed that intramuscular pressure was affected by the tightness of the fascial covering of the muscle. Therefore, the biceps muscle must be used for all measurements. If another muscle is used, the normal variations for that muscle must be determined. Wells *et al.*[6] have also published figures for intramuscular pressure on muscles of the lower extremities.

the muscle. At this point the reading is taken. The first reading is discarded and the average of the next three is recorded as the intramuscular pressure. By this technique, the maximum variations were within 5 to 10 mm. of water on subsequent readings. In this study, the pressure readings were made by the same team of two workers. One manipulated the pressure on the bulb, and the other obtained the critical point of movement of fluid in the capillary tube.

Measurements (320) of intramuscular pressure were made on 60 normals. The values varied between 60 to 90 mm. of water and corresponded with the published values of Henderson[3] and of Wells *et al.*[6]

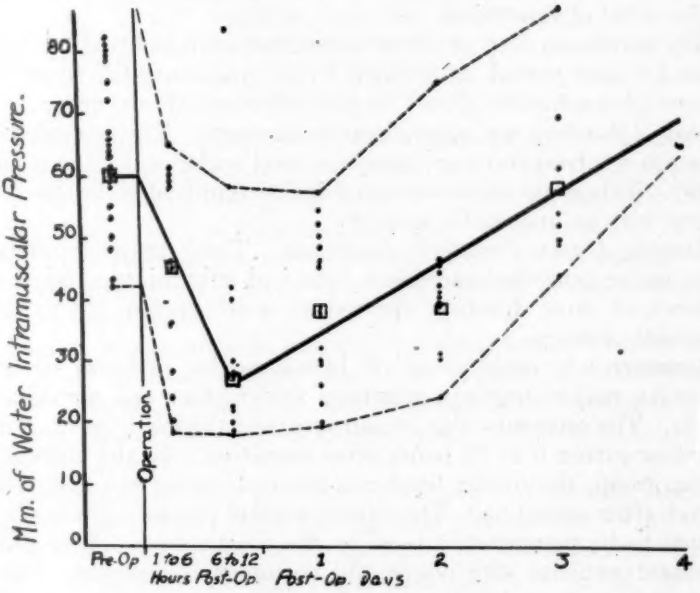


ETHER ANESTHESIA

CHART 2.—The effect on intramuscular pressure of surgery under ether anesthesia in the uncomplicated uneventful postoperative course. The broken lines indicate the limits of variations in intramuscular pressure. The heavy line shows the average values. The lowest level of intramuscular pressure was noted during the first 6-hour postoperative period. A return to the preoperative level was obtained by the fourth day after operation.

The Effect of Surgery Under Ether Anesthesia. The effect of surgery under ether anesthesia was studied in 54 observations on 12 patients. Most of these were on the gynecologic service. The routine measures consisted of morphine sulphate and atropine sulphate in the preparation for anesthesia. Morphine sulphate was administered every 4 hours as needed postoperatively. Intravenous fluids chiefly of 5% glucose in saline, were administered as indicated. Carbon dioxide inhalations of the gas diluted in air were given as described by Gunther and Blond.[1] The inhalations were given at 15-minute intervals until the patient awakened; every half hour for

12 hours, and every hour during the second 12-hour period. The intervals were prolonged to from 2 to 4 hours during the next 24 to 48 hours as indicated. The inhalations were discontinued after 48 hours. No effort was made in this study to separate the effect of the various agents used in the pre- and postoperative routine. The results obtained are those of the composite picture of the routine postoperative course in this hospital. However, at a later date, these agents were studied separately on other patients. Their effect on intramuscular pressure was found to be negligible. These results will be reported in another communication.



SPINAL ANESTHESIA

CHART 3.—The effect on intramuscular pressure of surgery under spinal anesthesia, in the uncomplicated uneventful postoperative course. The broken lines indicate the limits of variation in intramuscular pressure. The heavy line shows the average values. The lowest level of intramuscular pressure was noted during the second 6-hour postoperative period. A return to the preoperative level was obtained by the fourth day after operation.

In the patients who followed the normal, uneventful course of postoperative convalescence, a marked drop in the intramuscular pressure was observed during the first 6 hours of the postoperative period. The maximum lowering occurred at 6 hours. In the second 6-hour period, a slight rise was noted. Every patient operated upon under ether anesthesia showed a drop of intramuscular pressure to a level of from 20 to 40 mm. of water in the first 12 hours. The intramuscular pressure gradually returned to its preoperative level

during the next 4 days (Chart 1). During the excitement stage of ether anesthesia both intramuscular and venous pressures increased.

The Effect of Surgery Under Spinal Anesthesia. The effect of surgery under spinal anesthesia was studied in 130 observations on 32 patients. Most of these were from the general surgical service. The surgical procedures undergone by this group were far more formidable than in the group operated upon under ether anesthesia. The routine pre- and postoperative treatment was, however, identical (Chart 2). The anesthetic agent consisted of from 100 to 150 mg. of procain or its equivalent dosage in pantocain, or their mixtures as indicated by the need for prolonged anesthesia or a higher level of anesthesia.

The maximum drop of intramuscular pressure occurred during the second 6-hour period, in contrast to the maximum fall in the first 6-hour postoperative period in the ether anesthesia group. The extent of the drop was approximately the same. The intramuscular pressure returned to its preoperative level within 4 days postoperatively. This group also represented the uncomplicated postoperative course with an uneventful recovery.

Surgery Under Pentothal Anesthesia. Three patients operated upon under pentothal anesthesia, who had only minor surgical procedures, of short duration, showed no postoperative fall in intramuscular pressure.

Summary. A rapid drop of intramuscular pressure occurred following major surgical procedures under ether and spinal anesthesia. The intramuscular pressure reached the low level of 20 mm. of water within 6 to 12 hours after operation. In the ether anesthesia group, the lowest level was reached during the first 6-hour period after operation. The intramuscular pressure gradually returned to its preoperative level by the fourth day. These groups represent patients with uneventful postoperative courses. Pulmonary atelectasis and other complications were not present. The return of the intramuscular pressure to normal levels paralleled the clinical improvement. Surgery of a minor nature, in 3 patients under pentothal anesthesia, was not followed by a drop of intramuscular pressure.

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INTRAMUSCULAR PRESSURE.

II. The Venopressor Mechanism in Shock-like Conditions and the Effects of Various Drugs.*

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In the foregoing article[6] we showed a fall in intramuscular pressure after major surgical procedures with a return to the preoperative level by the fourth postoperative day. This communication deals with the variations in intramuscular and venous pressures as they occurred in the postoperative complications of pulmonary compression (atelectasis), shock, infection, and in collapse following massive hemorrhage.

A fall in venous pressure and a decreased volume of venous return are among the most striking physiologic changes in the circulatory failure of shock. Among the most constant pathologic findings are the high, flaccid diaphragms, the red, oozing, atelectatic lungs, and the empty heart.[1,12,16]‡

The theoretical basis for these alterations in respiratory and circulatory function have been postulated by Henderson.[8] He believes that the lowered intramuscular pressure, or "muscle tonus"§ as he prefers to describe the phenomenon in shock, is one of the most important factors in the failure of the venopressor mechanism. The tonicity of the muscles of the body, he believes, is a factor of greater importance in the maintenance of the venous circulation than is that of the vasomotor mechanism. This relationship between "muscle tonus," *i. e.*, intramuscular pressure, venous pressure and the volume of flow in the venous system, he terms the "venopressor mechanism."

* Read before the staff of the Cedars of Lebanon Hospital, Los Angeles, Calif., May 20, 1940.

† Dr. Gunther is now in military service as Lieutenant-Commander, M.C., U.S.N.R.

‡ The theories advanced to explain the circulatory disturbances in shock,[12] such as the failure of the adrenal cortical hormone, disturbances in electrolyte balance, formation of the "H" substance, capillary damage and hemoconcentration, do not adequately explain the loss of intramuscular pressure, nor do they concern us here.

§ Johannes Müller, quoted by J. F. Fulton,[4] first employed the word "tonus" as *meaning a slight contractile tension characteristic of normal skeletal muscle when at rest*, and he attributed this tension to the influence continually exerted upon the muscle by the nerve centers in the brain.

An agent which would increase the lowered intramuscular pressure to normal should also elevate venous pressure and restore venous flow. Furthermore, a restoration of the values of both of these physiologic functions, should be accompanied by clinical improvement in shock-like conditions. Such an agent should be a valuable adjunct in the treatment of shock.

In this study we wish to report our observations on the intramuscular and venous pressures, and the altogether unexpected and startling alterations in respiratory functions, venous and intramuscular pressure after the use of certain drugs.

Methods and Controls. The intramuscular pressure was measured with Henderson's *apparatus as modified by Kerr and Scott.*[10] The sources of experimental error are discussed by Wells and Youmans[17] as well as by us.[6] The venous pressure was determined by the direct method. The auricular level was taken as being 5 cm. below the surface of the chest in the fourth interspace. The preoperative measures consisted of morphine and atropine sulphate in the preparation for anesthesia. Morphine sulphate was given every 4 hours as needed in the postoperative period for the control of pain. Fluids were administered intravenously as needed to combat dehydration and acetone ketosis. The fluids were chiefly 5% glucose in saline, or physiologic saline. Inhalations of carbon dioxide gas, diluted in air, were given as described by Gunther and Blond.[5] The inhalations were given at 15-minute intervals until the patient awakened; every half-hour for 12 hours and every hour during the second 12-hour period. The interval was prolonged to from 2 to 4 hours during the next 24 to 48 hours.

The Separate Effect of the Different Drugs and Agents Used in the Pre- and Postoperative Routine. Morphine sulphate (gr. $\frac{1}{4}$) and atropine sulphate (gr. 1/150) were administered subcutaneously to 5 patients several days before elective surgery. No changes were noted beyond the usual 10 mm. error in reading the pressures, during a 4-hour period. Neither were changes obtained during and following the administration of from 1 to 2 liters of fluids, saline or 5% glucose intravenously in 44 observations, or of blood transfusions in 8 observations.

Despite the routine administration of carbon dioxide gas during the postoperative period, a marked lowering of the intramuscular pressure occurred. To study the effect of carbon dioxide inhalations in a markedly depressed level of intramuscular pressure, inhalations of the gas to the point of marked hyperpnea were given to 3 patients. The lowered level of intramuscular pressure did not change following the administration of the gas.

Postoperative Complications. The individual case reports herein, represent a group of patients with postoperative complications. These were atelectasis, evisceration, shock and peritonitis. The effects of hemorrhage, blood transfusion, caffeine sodium benzoate, paredrine and of pyridine-beta-carboxylic acid diethylamide,* will be shown in the individual case reports.

* For the 25% solution of pyridine-beta-carboxylic acid diethylamide used in this study, we are indebted to the Ciba Pharmaceutical Products, Inc., who supplied this substance known under the trade name of Coramine. For the sake of brevity we will refer to the trade name of the drug.

Coramine has been used as a respiratory stimulant. It appears to act either on the respiratory center or on the afferent nerve endings in the carotid bulb. Henderson has pointed out that the nervous mechanism of respiration exerts a powerful influence

The effect of Coramine, CO_2 inhalation and the intravenous administration of glucose in the usual and uncomplicated postoperative course is shown in Table 1.

TABLE 1.—EFFECT OF SURGERY ON INTRAMUSCULAR PRESSURE AND THE EFFECT OF THE INTRAVENOUS ADMINISTRATION OF 5% GLUCOSE, OF THE INTRAMUSCULAR ADMINISTRATION OF CAFFEIN SODIUM BENZOATE, OF THE INTRAVENOUS ADMINISTRATION OF CORAMINE, OF THE SUBCUTANEOUS INJECTION OF STRYCHNINE SULPHATE AND OF THE INHALATION OF CARBON DIOXIDE GAS DILUTED IN AIR, ON A LOWERED LEVEL OF INTRAMUSCULAR PRESSURE.

Patient. H. P.		M. H.	M.	A. G.	H. E.	
Intramuscular pressure, mm. H_2O.	Venous pressure, cm. H_2O.	Intramuscular pressure, mm. H_2O.	Intramuscular pressure, mm. H_2O.	Intramuscular pressure, mm. H_2O.	Intramuscular pressure, mm. H_2O.	
54	—	81	49	76	—	Before surgery.
29	10	57	19	—	—	1 hour after surgery.
—	—	—	—	43	—	3d day after surgery.
..	..	..	..	..	..	2000 cc. 5% glucose intravenously. Readings immediately after glucose and 6 hours after surgery.
25	5	—	—	—	—	
—	—	42	—	—	—	6 hours and 30 minutes after surgery.
—	—	31	28	43	—	Before administration of 7½ grs. caffein sodium benzoate given intramuscularly.
—	—	40	26	54	—	30 to 40 minutes later.
25	5	40	19	21	20	Before administration of 5 cc. Coramine intravenously.
49	6	51*	38	71	59	5 minutes after injection.
61	—	—	—	—	—	30 minutes later.
—	—	—	32	73	—	1 hour after injection.
—	—	—	28	—	26	Before administration of strychnine sulphate, gr. $\frac{1}{30}$ subcutaneously.†
—	—	—	26	—	20	1 hour after injection.
61	—	—	—	—	—	Before administration of inhalations of CO_2 gas diluted in air.†
59	—	—	—	—	—	Immediately after hyperpnea.

* Intramuscularly.

† Additional data on normals will be shown in another communication.

on "muscle tonus." The pharmacology of Coramine has been discussed fully by Meier and Müller.[11]

There is practically no danger of overdosage with Coramine, inasmuch as the toxicity is low. Furthermore, the drug carries a warning signal when the injection should be stopped, by the appearance of coughing. Even if the warning signal of cough is missed, a second warning appears in the form of mild muscular convulsions which are not serious to the patient. Convulsions appear long before the lethal dose is approached.[15] We have administered as much as 30 cc. of Coramine in divided doses intravenously, within a 30-minute period to normal individuals. The only unpleasant reaction of the large dosage in normals consisted of a marked pressor effect with headache and sneezing. The pressor action seen on normals was not obtained in patients in shock-like conditions.

Case Reports. CASE 1. H. P., female, aged 42, had a supravaginal hysterectomy. Immediately after surgery, when the patient had been returned to her room the intramuscular pressure was obtained at the low level of 29 mm. of water. Five centimeters of Coramine were given intravenously. The characteristic respiratory stimulation consisting of deep and rapid inhalations, accompanied by flushing of the skin was immediate and prompt. The intramuscular pressure was obtained at 49 mm. of water, a rise of 20 mm.*

The administration of 2000 cc. of 5% glucose intravenously, and the inhalations of carbon dioxide gas in the usual postoperative procedure did not alter the level of the intramuscular pressure. The Coramine effect wore off in 5 hours and the intramuscular pressure again dropped to a low level. The patient made an uneventful recovery pursuing the usual uncomplicated postoperative course.[6]

On three occasions, the development of clinical atelectasis was observed after surgery, in shock states, accompanied by greatly lowered levels of intramuscular pressure.

CASE 2. J. S., a 58-year-old male had a partial gastrectomy for the removal of a carcinoma. The intramuscular pressure values fell steadily through the first 3 postoperative days. On the eighth postoperative day the viscera protruded through the wound. Three hours after the secondary wound closure, the intramuscular pressure dropped to 20 mm. of water (Chart 1). The venous pressure was found at the extremely low level of 1 cm. of water. The patient was stuporous and dyspneic. The pulse was rapid and thready. The face was pale and pinched and sweating was profuse. The vital signs were: pulse 160 and respirations 62 per minute, temperature 104° F., and blood pressure 140/80. The clinical picture was that of peripheral failure, or shock with vasomotor compensation maintained (compensated forward failure; Harrison[7]).

Percussion of the chest showed relative liver dullness on the right at the third rib anteriorly and flatness below the third interspace, with a corresponding level on the left. The breath sounds were suppressed and fine crepitant râles were audible at both lung bases. These physical findings were compatible with those of postoperative pulmonary atelectasis (more strictly pulmonary compression), and are frequently misdiagnosed as postoperative pneumonia.

Two doses of Coramine of 4.5 cc. each were given without results.† Following the administration of a subsequent dose of 10 cc. Coramine, the patient awakened from his stupor, became restless and 15 minutes later, when taken, there was noted a rise in the intramuscular pressure to 53 mm. of water. The rise in the venous pressure paralleled the rise of intramuscular pressure and was obtained at 12 cm. of water. Within the next 30 minutes

* Measurement of intramuscular pressure, after intravenous administration of a drug, especially in the instances where Coramine was given, was made as rapidly thereafter as technically possible. Readings of intramuscular pressure were obtained within 2 to 3 minutes, and in no instance did it take longer than 5 minutes from the time of administration of the drug.

† This was our first experience of a failure to obtain the immediate respiratory response following the intravenous administration of Coramine, in doses of 4.5 cc. Later when we studied normal individuals we found that the immediate respiratory stimulation was occasionally not obtained with the smaller dose of 4.5 cc. If, however, it was followed by the administration of the larger dose of 10 cc. the characteristic prompt hyperpnea ensued. As will be shown in another communication the spectacular increase of low intramuscular and venous pressures was not obtained when their values were within normal levels at the outset.

the physical signs in the chest changed. The percussion note of relative liver dullness was obtained at the fifth interspace and the breath sounds became audible, of a harsh bronchovesicular quality. The disappearance of the pulmonary compression and the descent of liver dullness, presumably the diaphragm level, was as spectacular as the changes in the intramuscular and venous pressures. During these events the blood pressure which was 135/80 remained unaltered.*

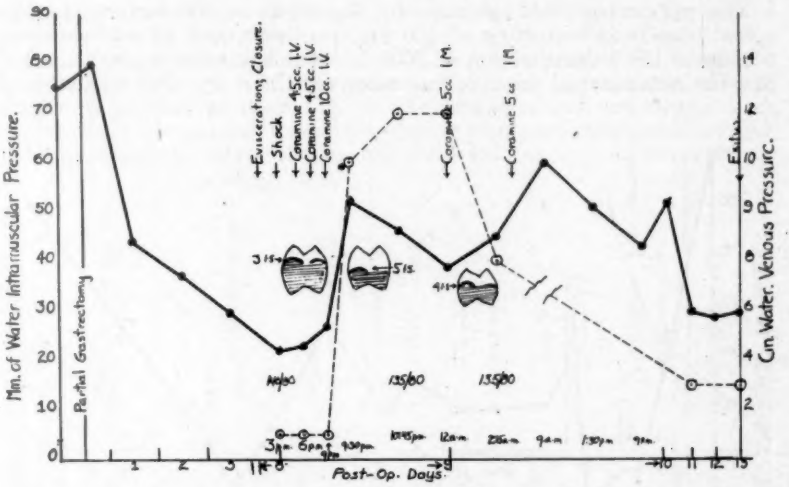

CHART 1.—Appearance of bilateral pulmonary compression (atelectasis) concomitant with the fall of the intramuscular and venous pressures in surgical shock. The administration of Coramine intravenously was followed by an immediate and marked increase in intramuscular and venous pressures. A change in the physical signs in the chest appeared within 30 minutes. The signs of pulmonary compression disappeared.

The intramuscular pressure remained at a high level during the period of two subsequent administrations of Coramine given at 3-hourly intervals by the intramuscular route. The following morning, the general condition of the patient was decidedly improved. The pulse was 120 and the respirations 32 per minute. The temperature was 99.6° F. The clinical picture of forward failure and of atelectasis had disappeared.

Infection of the peritoneal cavity developed, and during the next 11 days, the intramuscular pressure values slowly dropped and peripheral circulatory

* Postoperative pulmonary atelectasis may disappear with great rapidity following many different measures, or without any obvious reason. It is likely, that in our first cases we were dealing with "pulmonary compression" with an elevation of the diaphragms, as described by Müller *et al.*[13] and Prinzmetal *et al.*,[14] rather than with true atelectasis which according to the definition of Coryllos,[3] requires pulmonary compression and bronchial obstruction. In our third observation of this condition, the respiratory response was accompanied by a severe coughing paroxysm, after which large quantities of purulent sputum were expectorated. In this instance, true atelectasis was probably present. However, from the clinical point of view, the picture of atelectasis with bronchial obstruction, as determined solely by physical and vital signs, cannot easily be differentiated from simple pulmonary compression and elevation of the diaphragms. Sufficient Roentgen ray observations have been made in papers,[2,9,13] under similar circumstances, and in one of our cases to give authoritative weight to our observations by physical methods, relative to changes in position of the diaphragm.

collapse again appeared. Evisceration occurred again on the thirteenth day and he died shortly thereafter. The natural course of the illness was followed during the later period without further attempt to alter either the intramuscular or venous pressures.

CASE 3. S. B., age 33, female, gave us the opportunity to study the effects of intravenous fluids, the inhalations of carbon dioxide gas, the effect of the intramuscular administration of caffein sodium benzoate and the intravenous administration of Coramine.

This patient had renal tuberculosis. Nephrectomy was performed under spinal anesthesia consisting of 100 mg. pantocain and 80 mg. procaine.

Despite the administration of 2000 cc. of intravenous fluids, a marked drop of intramuscular pressure was observed (Chart 2). The inhalation of

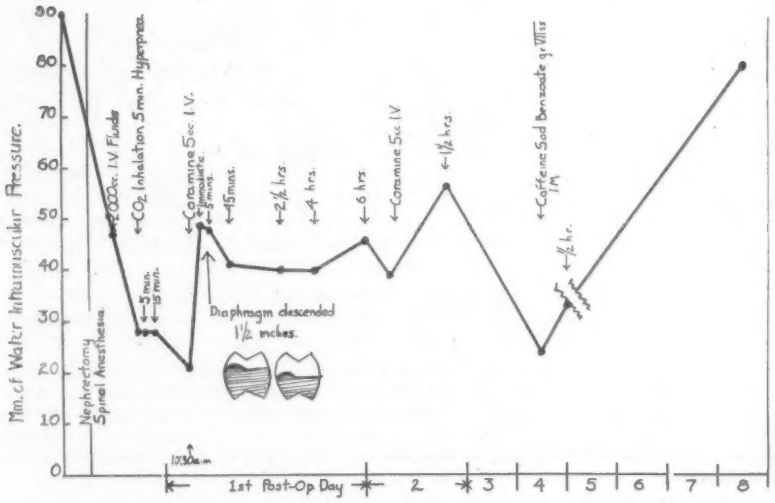

CHART 2.—A fall in intramuscular pressure, following nephrectomy, despite the intravenous administration of fluids, and of carbon dioxide inhalation to the point of hyperpnea. Concomitant with the fall of intramuscular pressure, the clinical picture of bilateral pulmonary compression (atelectasis) developed. Following the intravenous administration of Coramine, an immediate and marked increase in the intramuscular pressure occurred. The physical signs of pulmonary compression disappeared within 45 minutes. A very slight increase in intramuscular pressure followed the administration of caffein sodium benzoate.

carbon dioxide gas for 5 minutes to the point of marked hyperpnea did not raise the level of the depressed intramuscular pressure. On two occasions, an intravenous injection of Coramine was followed by a marked rise of the intramuscular pressure. On the fourth postoperative day 7½ gr. of caffein sodium benzoate was given intramuscularly and a slight increase in the intramuscular pressure was noted one half-hour later. From this point on, the patient made an uneventful recovery.

As in the previous patient, at the time when the level of the intramuscular pressure was severely depressed, coincidentally, pulmonary complications were noted. The physical signs of pulmonary compression, and the clinical picture of bilateral pulmonary atelectasis at the bases were noted. The pulse was 120 and respirations 30 per minute. The temperature was 100.4° F.

Following the administration of Coramine, a marked rise occurred in the intramuscular pressure. Simultaneously, the level of the diaphragms, determined by percussion of liver flatness on the right, and by percussion of the lower border of lung dullness on the left, moved downward 1½ inches. The lungs inflated, and the findings of pulmonary compression, and the clinical picture of atelectasis rapidly disappeared.

CASE 4. S. S., male, aged 54, had a cholecystectomy under inhalational anesthesia. When returned from the operating room, his intramuscular pressure was recorded at the low level of 21 mm. of water and the venous pressure at 7 cm. of water.

The blood pressure had fallen from 140 systolic and 100 diastolic to 74 systolic and 56 diastolic. The pulse was 140 and the respirations 20 per minute. The temperature was 98° F. The skin was cool, and covered with perspiration. The patient showed the clinical picture of postoperative shock with a failing vasomotor mechanism (forward failure, uncompensated).

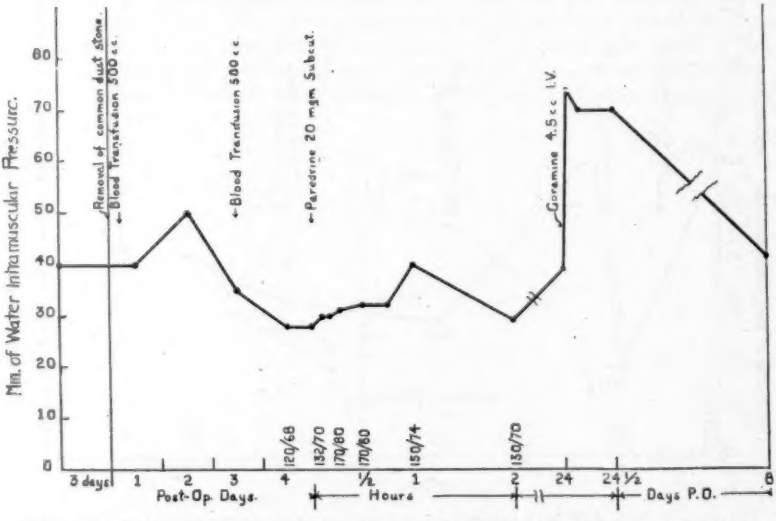

CHART 3.—The effects of blood transfusion, paredrine and of Coramine on intramuscular pressure. Despite two blood transfusions the intramuscular pressure fell to a low level. Following paredrine, the systolic blood pressure rose from 120 to 170 systolic, with no significant change in the intramuscular pressure level. Coramine given intravenously was followed by a marked and prompt increase in the intramuscular pressure.

Ten cubic centimeters of Coramine were given intravenously. Within 9 minutes the intramuscular pressure was recorded at 99 mm. of water and the venous pressure at 14 cm. of water. The skin became flushed and warm and the general appearance improved. Within 3 hours of the administration of the Coramine, the intramuscular pressure had fallen to 52 mm. of water and the venous pressure to 3.5 cm. of water.

On the fifteenth postoperative hour the intramuscular pressure was recorded at 54 mm. of water and the venous pressure at 5.5 cm. of water. The patient was again perspiring, the skin was cool, and his face pale. The pulse was 168 and the respirations 28 per minute. The temperature was 102.6° F. The blood pressure was 55 systolic and 30 diastolic, and he again showed the clinical picture of forward failure with failing compensation of the vasomotor mechanism.

The upper border of liver dullness was obtained by percussion at the 3d interspace and pulmonary dullness at a corresponding level on the left. The breath sounds were suppressed and practically inaudible at both bases. Râles were not heard. The physical signs of bilateral pulmonary compression and the clinical picture of bilateral pulmonary atelectasis were present. The elevation of the diaphragms and compression of the lungs were verified by Roentgen ray examination and were interpreted by the roentgenologist as pulmonary atelectasis.

On the sixteenth postoperative hour, 5 cc. of Coramine were given intravenously. The first readings recorded 4 minutes later showed intramuscular pressure at 99 mm. of water and venous pressure at 13 cm. of water. After 12 minutes the intramuscular pressure stabilized between 63 and 72 mm. of water and the venous pressure between 7 and 8 cm. of water. These levels were recorded during the next 20 minutes.

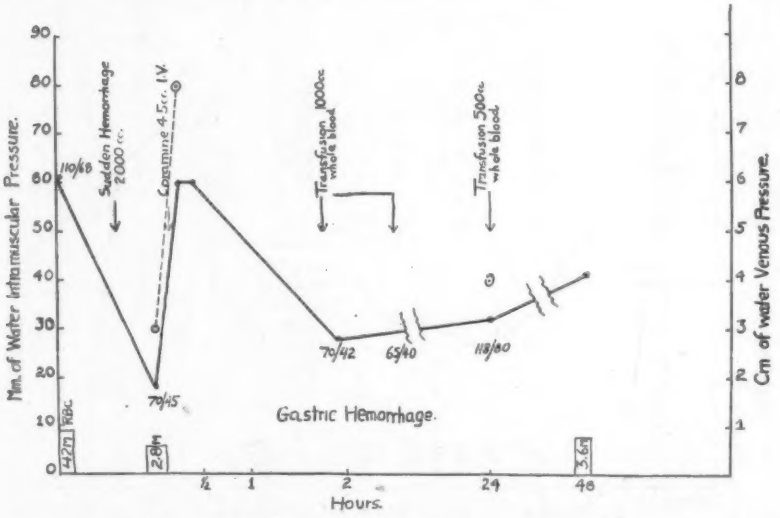

CHART 4.—The fall in intramuscular pressure, venous pressure, and of arterial pressure following a massive gastric hemorrhage associated with peripheral collapse. The administration of Coramine was followed by a prompt and marked increase in both intramuscular and venous pressures. Arterial pressure remained unchanged. Transfusion of blood did not significantly alter the levels of intramuscular pressure.

Immediately following the administration of the Coramine the patient became restless, his color changed to a flush, and he had several paroxysms of coughing, which were accompanied by the expectoration of a small "kidney basin" full of thick, tenacious greenish-yellow material.

Percussion of the lungs 22 minutes after the administration of the Coramine showed the upper border of the liver dullness at the 5th interspace with a corresponding level of pulmonary dullness on the left. Breath sounds were audible, of a harsh bronchovesicular quality, and many fine râles were audible at both bases.

The following morning, *i. e.*, 12 hours after the administration of the Coramine, the intramuscular pressure was recorded at 51 mm. of water and the venous pressure at 5.4 cm. of water. The temperature was 100° F. The pulse 130 and the respirations 30. The physical signs of incomplete aëration were still present at the bases and were verified by Roentgen ray,

but the general condition of the patient had improved and the clinical picture of forward failure was no longer present. The patient developed a pulmonary abscess in the upper right lobe which was diagnosed 19 days after surgery. The clinical picture of shock never returned.

Intramuscular Pressure During Infection. The effect of severe infection was observed in 3 patients. The intramuscular pressure fell to a low level, similarly as was seen in the patient with postoperative depression, shock, or after hemorrhage with shock.

CASE 5. H. E., female, aged 56, was operated for acute appendicitis with rupture. Diffuse peritonitis developed. The intramuscular pressure shown in Table 1, was at the low level of 36 mm. at the time of operation and dropped to 22 mm. where it remained until the second postoperative day when Coramine was administered.

CASE 6. A. G., male, aged 60, was operated for mastoid infection due to pneumococcus Type III. The preoperative intramuscular pressure was 80 mm. and 72 mm. the day of operation. Four days later with a full picture of meningitis, septicemia and heart failure, the intramuscular pressure had fallen to 21 mm. The clinical picture was that of severe toxemia

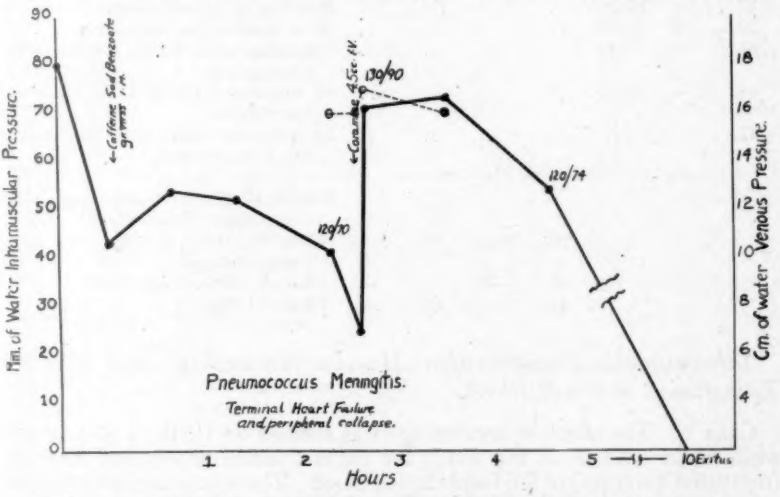

CHART 5.—The effect of caffein sodium benzoate on a lowered intramuscular pressure, and the drop in intramuscular pressure during the depression of acute infection. The intravenous administration of Coramine was followed by a prompt and marked increase in intramuscular pressure.

and shock (Chart 5; Table 1). In J. S. (Case 2; Chart 1), as the peripheral failure appeared during the progress of peritonitis, the values for intramuscular and venous pressures both fell to low levels. However, in A. G. (Chart 5) both peripheral failure (associated with acute toxemia) and congestive heart failure are represented. The intramuscular pressure at the height of the infection was at the low level of 20 mm. of water and the venous pressure was at the high level of 16 cm. of water.*

* We have also observed the combination of normal values for venous pressure and low levels for intramuscular pressure in patients with acute coronary thrombosis, with shock, without congestive heart failure. Intramuscular pressure after coronary occlusion will be the subject of another communication.

The response of a lowered intramuscular pressure to the intravenous administration of Coramine in all three examples of the depression of infection was as prompt, spectacular and of a similar magnitude seen after its administration in the collapse of massive hemorrhage or in shock states (Charts 1, 4, 5; Table 2).*

TABLE 2.—EFFECT OF MASSIVE HEMORRHAGE ON INTRAMUSCULAR PRESSURE AND THE EFFECT OF CORAMINE AND BLOOD TRANSFUSION ON A LOWERED LEVEL OF INTRAMUSCULAR PRESSURE AFTER HEMORRHAGE.

Patient. A. S. Intramuscular pressure, mm. H_2O.	A. S. Venous pressure, cm. H_2O.	A. S. Blood pressure, mm. Hg.	R. F. Intramuscular pressure, mm. H_2O.	R. F. Blood pressure, mm. Hg.	R. F. Hgb., % Sahli.	R. F. R.B.C., million.	
37	—	125/65	..	..	..	..	Bleeding duodenal ulcer.
20	3	70/30	..	..	..	..	After massive hemorrhage.
65	8	78/42	..	..	..	..	3 minutes after 4.5 cc. Coramine intravenously.
48	—	92/60	..	..	..	..	40 minutes later and before blood transfusion.
47	—	—	..	..	..	..	Immediately after 500 cc. whole blood transfusion.
							Duodenal ulcer: hemorrhage with spontaneous recovery.
			20	98/60	66	3.59	Feb. 6, 1940, 8 P.M. after large hemorrhage.
			43	—	—	—	Feb. 7, 1940, 1 P.M.
			47	—	64	—	Feb. 8, 1940.

Intramuscular Pressure after Massive Hemorrhage, and after the Transfusion of Whole Blood.

CASE 7. The effect of hemorrhage was studied on H. R., a 57-year-old white male. While on the ward, the patient suddenly vomited 2000 cc. (measured quantity) of fluid and clotted blood. The intramuscular pressure, venous pressure and the blood pressure were all recorded at a low level following the hemorrhage (Chart 4). The patient was in profound collapse. Immediately after the intravenous administration of 5 cc. of Coramine a marked rise in intramuscular and venous pressures and improvement in the clinical condition were noted. The blood pressure remained unaltered. The increase in intramuscular and venous pressures was not maintained, and 2 hours later the intramuscular pressure was again recorded at a low level. Following a blood transfusion of 1000 cc. of whole blood, no significant increase in intramuscular pressure could be recorded.

CASE 8. A. S., aged 26, suffered a sudden hemorrhage from a bleeding duodenal ulcer. Likewise, the blood pressure, venous pressure and intramuscular pressure fell to low levels (Table 2). An intravenous injection of

* The venous pressure in Chart 5, which was already high due to the backward failure (congestive heart failure), changed slightly, a variation within the error of the method, whereas the intramuscular pressure rose markedly after the administration of Coramine.

4.5 cc. of Coramine was followed by an immediate rise in venous and intramuscular pressures. A transfusion of 500 cc. of whole blood showed no change in the value of intramuscular pressure before or after the transfusion.

CASE 9. R. F., a 41-year-old female, similarly suffered a sudden hemorrhage from a bleeding duodenal ulcer (Table 2). She likewise showed low values for intramuscular pressure following the hemorrhage.

CASE 10. E. F., a 57-year old female (Fig. 3). Following the removal of a common duct stone, the intramuscular pressure continued to fall, despite two blood transfusions of 500 cc. each. On the fourth postoperative day the intramuscular pressure was recorded at the low level of 28 mm. of water. Paredrine,* 20 mg., was given subcutaneously. No significant change in the intramuscular pressure was noted over a 2-hour period. The blood pressure, however, rose from 120 systolic to 170. In contrast, 4.5 cc. of Coramine, given intravenously the next day, was followed by a marked rise in intramuscular pressure (Table 3).

TABLE 3.—EFFECT OF PAREDRINE AND CORAMINE ON A LOWERED LEVEL OF OF INTRAMUSCULAR PRESSURE.

E. F.		
Intramuscular pressure, mm. H_2O.	Blood pressure, mm. Hg.	
28	130/68	April 20, 1940, 3.30 P.M., 20 mg. paradrine subcutaneously.
31	132/70	5 minutes later.
29	162/74	10 minutes later.
31	170/80	15 minutes later.
33	170/80	30 minutes later.
32	165/74	45 minutes later.
41	150/74	60 minutes later.
29	130/70	2 hours later.
39	..	April 21, 3.30 P.M., before 5 cc. Coramine intravenously.
73	..	2 minutes later.
70	..	5 minutes later.
70	..	30 minutes later.
41	..	April 24.

The lack of response after transfusion of whole blood was also seen in 3 other patients whose case histories are omitted for brevity. A total of 8 observations showed no change in the values of intramuscular pressure after the transfusion of blood, whereas the administration of 4.5 cc. of Coramine by the intravenous route, was in each instance followed by a prompt increase in its level.

Intramuscular Pressure Responses to Caffein Sodium Benzoate, Strychnine, Paredrine and Ephedrine. Six patients were studied for the effect of caffein sodium benzoate (Charts 1, 2, 5; Table 1.) The intramuscular administration of 7½ grains of this drug was followed by a definite, although slight increase in intramuscular pressure in 4 of the 6 instances.

* The Paredrine was supplied through the courtesy of Dr. M. H. Nathanson.

The increase in intramuscular pressure was about 10 mm. of water and is theoretically within the variations of error of the method. However, all changes after caffein were in the same upward direction.

Paredrine (20 mg. subcutaneously) was given to 5 patients and ephedrine sulphate ($\frac{3}{4}$ gr.) in 1 patient during the course of spinal anesthesia. Paredrine (20 mg. subcutaneously) was given to 4 normal patients solely to study its effect on intramuscular pressure. Detailed figures are shown of a patient with low initial intramuscular pressure in Table 3 and in Chart 3.

The pressor action of Coramine which was seen in normals, was not observed by us in shock-like states wherein the intramuscular pressure was at a low level, whereas its ability to raise intramuscular pressure and venous pressure in these conditions was a constant phenomenon. In contradistinction: paredrine in addition to its pressor action, is also a venoconstrictor. It raises venous pressure for a very short time although it has no effect on a low intramuscular pressure. No attempt was made in these studies to bolster a failing vasomotor mechanism with an additional pressor substance such as paredrine. The combined action of venopressor and vasomotor drugs in shock-like states should be a physiologically sound therapeutic procedure. In no instance when given to patients under spinal anesthetic did paredrine or ephedrine prevent the fall in intramuscular pressure which has been observed following surgical procedures,[6] nor did it alter the intramuscular pressure levels in the normals studied specifically for its effect. The administration of strychnine sulphate (gr. $\frac{1}{30}$ subcutaneously) (Table 1) likewise did not alter the intramuscular pressure.

Summary and Conclusion. Intramuscular pressure measurements were made in a variety of clinical conditions and in normal patients. In the postoperative depression following major surgery under either spinal or ether anesthesia, in the collapse following severe hemorrhage, in the depression of severe infection, and in postoperative shock, a lowered intramuscular and venous pressure was a constant observation.

Morphine, atropine, strychnine, paredrine and carbon dioxide gas, did not alter a lowered intramuscular pressure. Although paredrine constricts veins and increases venous pressure, its administration did not prevent the fall in intramuscular pressure following surgery under spinal anesthesia, nor did it raise a lowered intramuscular pressure. The intravenous infusion of fluids, glucose, saline and transfusion of blood did not alter a lowered intramuscular pressure.

Pyridine-beta-carboxylic acid diethylamide (Coramine—Ciba) was the only chemical among those tested that consistently increased the levels of intramuscular and venous pressures simultaneously. Respiration was immediately stimulated and a productive cough appeared. If in coma, the patient became semi-conscious or con-

scious. In 3 patients in severe postoperative depression, physical signs clinically indistinguishable from atelectasis disappeared with great rapidity after the administration of Coramine. This phenomenon was coincident with the restoration to normal of intramuscular and venous pressure. The clinical improvement that followed its administration in the shock-like states was most gratifying. The data presented herein support Henderson's postulates of the venopressor mechanism.

There is practically no danger of overdosage with Coramine, as the toxicity is low. Also the drug carries a warning signal, coughing and later convulsive movements long before a lethal dose is approached.

Coramine in adequate doses appears to be a valuable adjunct in the treatment of the immediate period of shock-like conditions. The improvement, of several hours' duration, affords sufficient time to enable the patient to receive the benefits of whole blood, plasma, serum, vasomotor drugs, or other useful procedures.

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BOOK REVIEWS AND NOTICES

NATIVE AFRICAN MEDICINE, With Special Reference to Its Practice in the Mano Tribe of Liberia. By GEORGE WAY HARLEY, M.D., Ganta Dispensary, Liberia. Pp. 294; Frontispiece. Cambridge, Mass.: Harvard University Press, 1941. Price. $3.50.

EQUATORIAL and northern Africa have been brought to the fore by circumstances which are still waxing. We shall doubtless hear much about these regions, including matters medical, that is fanciful or untrue. Here we have something that is neither—it is the simple, objective story of the Mano people of northeastern Liberia and French West Africa, a story written by a medical missionary who has lived for 20 years almost exclusively among the blacks, by whom he is widely revered as a great healer. Thus, Dr. Harley has had unequalled opportunity to observe and comprehend the minds and customs of the relatively untouched natives.

Having collected the native names of 102 medicinal plants used for medical purposes, Dr. Harley was able, when back in this country on furlough, to identify many of them botanically, and also to perfect his general knowledge of African native culture. This led to an ethnologic study, over many years, especially of the secret society, the Poro Bush, which initiated the Mano youth into agricultural and political as well as magical arts.

The Mano concept of disease is here thoroughly discussed. In one of the longer chapters their rational treatment of disease is considered; but it is also shown how this logically accompanies magical treatment in the Mano mind, in some cases a mixture of the two being used. It has been especially interesting to the Reviewer to note the many similarities of customs with other primitive tribes, quite unrelated geographically, chronologically, and ethnographically (*e. g.*, the North American Indians). The medicine man, he who knows how to control mysteries, makes medicine for all human contingencies, sickness among the rest. For the sick, he uses rational remedies as readily as we do, but he must also divine and exorcise, with fetishes and ceremonies, that are just as logical to him as the purge or the splint.

This book, as a serious, well-documented study, is, to be sure, not light reading for the casual reader, nor was it meant to be. Even he, however, will find much to entertain him, a judicious selection being helped by a full index. For the anthropologist, the medical missionary, and the physician interested in primitive medicine, an intimate acquaintance with this valuable study is most warmly recommended. E. K.

TEXTBOOK OF CLINICAL PARASITOLOGY. By DAVID L. BELDING, M.D., Professor of Bacteriology and Experimental Pathology, Boston University School of Medicine; Member of Staff of Evans Memorial, Massachusetts Memorial Hospitals. Pp. 888, 3 plates. New York: D. Appleton-Century Company, 1942. Price, $8.50.

AT the present time there are available at least two adequate and modern textbooks of Parasitology, one of them having the same title as this now under review, not to mention a "handbook" or two, or the more extensive treatises on tropical diseases. While these publications do not preclude the possibility of improvement or of competition, additional publications in this field should have more to recommend them than voluminous repetition. The present volume appears to offer little more than that. The arrange-

ment of material impresses this Reviewer as awkward, with information scattered in several subdivisions. Often, too, the author seems entirely uncritical, tending always to build up when the best evidence does not warrant it. The book does not compare with others in its field.

H. R.

DISEASES OF THE SKIN. By FRANK CROZER KNOWLES, M.D., EDWARD F. CORSON, M.D., and HENRY B. DECKER, M.D. Pp. 621; 272 illustrations. Fourth Edition. Philadelphia: Lea & Febiger, 1942. Price, $7.00.

THE author and his collaborators, in this fourth edition, have completely revised, reorganized and modernized the text, have included additional topics, and have eliminated non-essential and out-dated material. For the most part, standard views on dermatology are expressed.

As it stands, this book is a convenient, terse, and well-illustrated text for students and practitioners. Among the especially good features are the listing of the regional distribution of common skin diseases, the various differential tables, doses in both metric and apothecary systems, and selected recent references for further consultation.

There are relatively few errata in this text. Two such are the continued use of "hereditary syphilis" (p. 414) for "congenital syphilis," which term is also used; and, on page 299 under "Xeroderma pigmentosum," Figure 95 is labeled "Xeroderma pigmentosa."

This edition further ensures the already established place of this work among the practical American texts on dermatology. H. B.

MANUAL DE LABORATORIS DE SALUD PUBLICA. By OSCAR COSTA-MANDRY, M.D., C.T.M., Director of the Public Health Laboratories of the Department of Health of Puerto Rico; Associate Professor of Epidemiology in the School of Tropical Medicine of the University of Puerto Rico under the auspices of Columbia University; Consultant in Clinical Pathology to the District Hospitals of Puerto Rico; Director of the Laboratory of the Mimiya Hospital of Santurce; and Secretary-Treasurer and Examiner in Pathological Anatomy and Bacteriology, Medical Examining Board of Puerto Rico. With a Foreword by P. MORALES OTERO, M.D., Acting Director and Associate Professor of Bacteriology and Immunology of the School of Tropical Medicine of the University of Puerto Rico. Pp. 368; 14 illustrations. San Juan: Dept. of Supplies, Printing and Transport., Govt. of Puerto Rico, 1941.

THIS laboratory manual for workers in the field of Public Health is the result of the author's experience of nearly 20 years in the manifold activities of Public Health laboratories in a tropical climate. Written not only for physicians but for lay workers, technicians and health officers, the book presents an unusual attention to details of procedure that should make it a welcome volume on every laboratory shelf in Spanish-speaking countries. The first section discusses the collection of samples; the second, the interpretation of results; the third, the procedures of technique; the fourth, the preparation of reagents and solutions, culture media, the techniques of sterilization, of filtration, of cleansing of apparatus; the care of laboratory animals; tables of weights and measures, etc. There are also appended the rules governing the functioning of the Public Health Laboratories and the laws which regulate the practice of technicians and microscopists in Puerto Rico. Well planned, written and indexed, this excellent book should find a wide appeal in all clinical laboratories, and especially in departments of public health in our sister republics to the South. R. K.

SCIENCE AND MAN. Twenty-four Original Essays by ALES HRDLICKA, REINHOLD NIEBUHR, JACQUES MARITAIN, ALFRED E. COHN, ARTHUR H. COMPTON, HAROLD C. UREY, WALDEMAR KAEMPFFERT, K. KOFFKA, BRAND BLANSHARD, JAMES T. SHOTWELL, CARL L. BECKER, JULIAN HUXLEY, BRONISLAW MALINOWSKI, FRANK KNIGHT, LEWIS MUMFORD, WALTER B. CANNON, KARL T. COMPTON, JEAN PIAGET, PHILIP C. JESSUP, HANS KELSEN, HAROLD D. LASSWELL, EDWIN G. CONKLIN, C. G. JUNG, RALPH BARTON PERRY. Edited with an introduction and conclusion by RUTH NANDA ANSHEN. Pp. 494. New York: Harcourt, Brace & Co., 1942. Price, $4.00.

THIS book is an effort—and a successful one—to study the place of science and its achievements in the world of man, with the aim, expressed by most of the contributors, implied at least by others, of harmonizing these achievements with man's essential humanity. Twenty-four essays, representing the scientific field from anthropology to zoölogy, present the different aspects of "the paths we must follow if science is to become the servant rather than the master of man." These are grouped in sections on: the material, methods and ends of science, the relation of science to the universe, to society, to internationalism, and to the individual, with chapters of introduction and conclusion by the Editor, who is also the editor of the Science and Culture Series.

Happily the day is now passed when Science and Religion (Faith) were regarded as necessarily incompatible. With the scientist's increasing knowledge of and dominance over his surroundings, he becomes, not paradoxically, more humble as to the vastness of his ignorance and the limitations of the scientific method. It is not so difficult, then, for him to recognize that we must continue to live in the midst of the unproved and the unprovable; and that philosophy and the various sciences, all necessarily proceeding by their own special methods, must work together as best they can to preserve man as a complete microcosm properly adapted to the macrocosm of our universe. Such are some of the thoughts evoked by perusal of these essays, and what could be more important for the solution of our present problems? One naturally finds some heavy going in unfamiliar fields, but there is also much valuable description of achievement as well as rational considerations of man's relation to science that are aimed to lead the way toward returning science to the service of man. E. K.

PSYCHOLOGICAL EFFECTS OF WAR ON CITIZEN AND SOLDIER. By R. D. GILLESPIE, M.D., Physician for Psychological Medicine, Guy's Hospital, London; Wing-Commander, Royal Air Force, Volunteer Reserve. Pp. 251. New York: W. W. Norton, 1942. Price, $2.75.

THIS is another volume to add to the growing library on psychosomatic medicine and can be read with profit by any physician who appreciates this rapidly expanding field of medicine. Quoting the author, "The book concerns itself with general principles and the issues that are raised by the occurrence of another world cataclysm, and refers especially to psychological aspects of its causation and to the question of what can be done to prevent in some fundamental fashion its repetition. This is largely a psychological problem and the experience of war itself, as it impinges on a whole community as this one does in a way never before known, not only fills gaps in our sociological past on what happens in peacetime, but is relevant to the advice that psychologists may give for the planning of the kind of new world that is to emerge after the war." The first half of the book discusses the changing concepts, constitutional and social factors in psychoneuroses. The second portion discusses psychoneuroses among civilians and members

of the fighting forces. Both halves are replete with examples and quotations from well-known men in the field.

The opening sentences of Chapter IV are of particularly interest; they express a general trend that runs through the book: "It can be said at once that one of the most striking things about the effects of the war on the civilian population has been the relative rarity of pathological mental disturbances among the civilians exposed to air raids. Guy's Hospital, which is situated in Southwark, is in the middle of one of the most frequently bombed areas of London, and in the midst of a large population area of the poorer classes. Yet the psychiatric out-patient department which still functions there records very few cases of neuroses attributable to war conditions." R. B.

FAMILY NUTRITION. A Monograph by Philadelphia Child Health Society. Pp. 106; 30 illustrations, 22 tables. Philadelphia, 1942. Price, free upon request.

THIS monograph covers acceptably the principles of modern nutrition and presents them in a form that will furnish to the teachers, social service workers, adult group workers, civic leaders, etc., for whom it is principally intended, information that they in turn can pass on to larger groups in schools and in the community.

It includes discussion of food requirements, the function of food, and the essentials furnished by different groups of foodstuffs. It is well illustrated and contains a number of sample menus for well-balanced meals, at various age levels. E. W.

ENDOCRINOLOGY: Clinical Application and Treatment. By AUGUST A. WERNER, M.D., F.A.C.P., Assistant Professor of Internal Medicine, St. Louis University School of Medicine; Associate Physician, St. Mary's Group of Hospitals; Physician, Endocrine Clinic, Desloge Hospital and the Missouri State Hospital No. 4, Farmington, Mo. Second Edition. Pp. 924; 327 illustrations, 1 colored plate. Philadelphia, Lea & Febiger, 1942. Price, $10.00.

THE first chapter reviews the autonomic nervous system, pointing out the importance of nervous as well as endocrine regulations in the body and noting the growing knowledge of neurohumoral relationships. This is followed by minor chapters on calorimetry, the glands in general and known and postulated hormones. In the section on the pituitary there are well-chosen tables and photographs showing osseous development from birth to maturity, age-height-weight tables, simple body measurements and body types. The author's classification of body types merges into descriptions of pituitary disorders. Here begin some of the 86 case histories, which throughout the book, serve to "highlight" the general description and enlarge its value as a diagnostic aid. Subsequent chapters present the gonads, lactation, the thyroid and parathyroid glands, the adrenals, pancreas, thymus and pineal, and so on. Short chapters on the relation of the endocrines to the skin, hair and teeth give recognition to commonly neglected minor aspects of this field. There is a short section on the diagnosis of endocrine conditions in children, in which connection the Reviewer notes with satisfaction the emphasis, in all parts of the book, on pediatric endocrinology.

The presentation of treatment is generally sound and concrete, in particular that on the care of adrenal insufficiency, and the menopausal syndrome. The author's work on involutional melancholia is well summarized.

There are occasional lapses from the general quality of this work. For example, in the preface the statement, "As a result of our present knowledge

of the functions of the ductless glands, the terms: neurasthenia, hypochondria and nervous breakdown are becoming obsolete" seems overoptimistic. The conclusion that testosterone relieves 50% to 70% of patients with prostatism is not supported by pathologic observation and would be unwarranted from the clinical data cited by the author on the preceding page. In the treatment of gonorrheal vaginitis in children, no mention is made of the use of sulfonamides which many prefer to estrogens. There is no mention of the recent studies on urinary ketosteroids which merit recognition in such a text, if only as the latest means of investigation.

The Reviewer concludes that there is no textbook of endocrinology comparable to the classic texts of Medicine, but that nevertheless he will frequently refer to Dr. Werner's book. It should be a distinct addition to the practitioner's library. F. L.

THE STRUCTURE OF PROTOPLASM. A Monograph of the American Society of Plant Physiologists. Edited by WILLIAM SEIFRIZ. Pp. 283; 74 illustrations, 1 portrait. Ames, Iowa: The Iowa State College Press, 1942. Price, $3.00.

THIS monograph is the printed record of a symposium on the Structure of Protoplasm presented under the auspices of the American Society of Plant Physiologists at Philadelphia on December 30, 1940, and is the first in what is planned to be a series of monographs published by this Society.

The volume deals with the modern concepts of the physical and chemical structure and properties of protoplasm, consisting of the following ten treatises: Microscopic Structure of the Cell Wall; Proteins and Protoplasmic Structure; Molecular Structure in Protoplasm; Some Mechanical Properties of Sols and Gels and Their Relation to Protoplasmic Structure; Structural Differentiation of Cytoplasm; Structural Differentiation of the Nucleus; Protoplasmic Streaming in Relation to Gel Structure in the Cytoplasm; The Relation of the Viscosity Changes of Protoplasm to Ameboid Locomotion and Cell Division; Physical Aspects of Protoplasmic Streaming; Some Physical Properties of Protoplasm and Their Bearing on Structure.

A supplement containing communications from Kurt H. Meyer of the University of Geneva and W. T. Astbury of the University of Leeds, deals with the chemical structure of protoplasm and the importance of elongated and folded polypeptide chains in biologic structure.

The book presents a fresh modern portrayal of protoplasmic structure and behavior and should prove of value to all workers and students in biology. D. C.

TIME AND THE PHYSICIAN. THE AUTOBIOGRAPHY OF LEWELLYS F. BARKER. Pp. 336; frontispiece, 7 illustrations. First Edition. New York: G. P. Putnam's Sons, 1942. Price, $3.50.

Details of the life of as able and versatile a man as Dr. Barker would necessarily be of interest on their own account; they are especially so when they happen to be interwoven with an important phase of medical development in this country and with a school and hospital that, though late arrivals, played such an important part in this development. Many will naturally turn first, therfore, to the early days of the Hopkins Medical School, and to the consideration of the 'full time" basis of clinical departments.

In 1902, in an address to some Hopkins alumni, Barker, then at Chicago, developed an idea that "Mall had told me" that the heads of clinical departments should be given salaries large enough to devote all their time to teaching and investigation freed from the distractions of private practice.

Unfortunately, however, when this procedure was put into effect at Hopkins in 1914, Barker, who had been head of the Department of Medicine there since 1905, was prevented by circumstances from being the first to apply the theory. In fact, like his successor, Janeway, and like Osler, he seems in his riper years to have modified considerably his views about the need for full time clinical teachers in all circumstances and localities.

In addition to the Hopkins sidelights, one reads with interest, in this entertaining work, of the author's Quaker childhood in Canada, of his Professorship of Anatomy at the University of Chicago, of the Commission to the Philippines, of plague studies in India and San Francisco, of advisory boards, committees, lectureships, memberships, honors, private practice, and the many items about which "it is given to only one man in a million to be really self-revelatory" (Jos. Collins). When one also considers how difficult it is, as Thales said, "To know one's self," the obstacles in the way of great autobiographies are obviously by no means insignificant.

E. K.

THE RAT IN LABORATORY INVESTIGATION. By JOHN Q. GRIFFITH, JR., M.D., and EDMOND J. FARRIS, PH.D. First Edition. Pp. 488; 178 illustrations. New York: J. B. Lippincott, 1942. Price, $7.50.

THIS is a very useful book for all who are engaged in work using the rat. Thirty authors supply valuable information, derived from their own experience, as well as data compiled from the literature. Many simple, effective diagrams complement photographic illustrations.

Subjects covered include anatomy and physiology; methods of housing; diet and metabolism; technique for various physiologic methods and surgical procedures; useful tables of drug dosage; spontaneous lesions, including parasites, infections and tumors; special methods for study of the nervous system. A section on pathologic changes in the teeth under experimental conditions is particularly interesting, because it is written by those trained in dentistry, has many excellent illustrations, and includes data obtained from dental publications not often consulted by the usual investigation. Data on endocrine aspects are quite brief and scattered and not as fully illustrated as other features.

This book is a real contribution in making easily accessible much useful information for laboratory workers.

I. Z.

A SYMPOSIUM ON RESPIRATORY ENZYMES. First Edition. Pp. 281; several illustrations. Madison, Wis.: The University of Wisconsin Press, 1942. Price, $3.00.

SOME thirty years ago when Casimir Funk coined the word "vitamin" to denote certain essential food constituents the entire knowledge of their chemical constitution could be summed up by an oversimplification in the word "amine." Today the chemistry of the vitamins roams over the entire field of organic chemistry and besides the "amines" of the B complex, such as pyridines, pyrimidines, thiazoles, alloxazines and nicotinamide, includes such diverse organic structures as ascorbic acid, polyene alcohols (A), sterols (D) and chromanes (E).

Alongside of the growth of our clinical knowledge of vitamins and their organic structure, there developed the field of the respiratory enzymes which concerned itself intimately with the chemistry of the intermediary metabolism of tissues. The discovery that essential constituents of these systems—co-enzymes—were in many instances identical with or closely related to the vitamins brought together these initially independent fields.

This fusion was fittingly celebrated in the autumn of 1941 by a combined symposium on "Respiratory Enzymes" and the "Vitamins" at the Universities of Wisconsin and Chicago. Each of 3 days' duration, they were attended by some hundred biochemists, physiologists and clinicians.

The book under review contains the papers delivered at Wisconsin which formed the chemical background for the subsequent vitamin symposium at Chicago. It illustrates how an independent rapidly growing basic science will contribute significant knowledge and help to a field of clinical medicine initially wholly unrelated.

The symposium includes discussions by the world's leading experts in the field and brings the subject of the respiratory enzymes up to the last minute in 1941. A broad interpretation of certain significant chapters is in place here. "Intermediate Carbohydrate Metabolism" (Otto Meyerhof) reviews the currently accepted views on the subject of carbohydrate breakdown in tissues. "Oxidative Mechanisms in Animal Tissues" (Eric Ball) treats in a general way the chemical means by which foodstuffs are oxidized and made to yield their energy. The subsymposium on "Hydrogen Transport" treats of the physico-chemical means by which hydrogen from the foodstuffs passes down the metabolic stream to its final combination with oxygen. The "Pasteur Effect" (Fritz Lipmann) discusses the chemistry of the aërobic and anaërobic metabolism of tissues. The discussion of "Nicotinamide" (Fritz Schlenk) shows how this important substance fits into the general scheme of metabolic co-enzymes. "Flavoproteins" (T. R. Hogness) gives the chemical background of the yellow enzymes and the related riboflavins. "Phosphorylations of Carbohydrates" (Carl Cori) again illustrates how an understanding of this fundamental mechanism is necessary for any comprehension of carbohydrate metabolism. "Metabolic Cycles" (E. A. Evans) gives the relations to tissue metabolism of the catalytic action of the 4 carbon dicarboxylic acids and of citric acid. These catalytic "cycles" have since projected themselves into discussions of cardiac embolism and aviation medicine. "Tumor Respiration" reviews the present status of this important subject. In the subsymposium on "Bacterial Respiration" is brought home again how fundamental understanding of bacterial metabolism paves the way for chemotherapy.

For the expert reader versed in chemistry and metabolism the book is unstintingly recommended. The general reader, unless he wishes to impose upon himself some weeks of arduous reading, must await the popular epitomization—still to be written—of this fascinating field. W. S.

INTERNATIONAL JOURNAL OF SEX-ECONOMY AND ORGONE-RESEARCH. Official Organ of the International Institute for Sex-Economy and Orgone-Research. Director: WILHELM REICH, M.D. Vol. I, No. 1. Editor: THEODORE P. WOLFE, M.D. New York: Orgone Institute Press, 1942. Price, $5 a year; single copies, $1.25.

THE purpose of this Journal is given as the publication of material relating to the theory and practice of sex-economy and to sex-economic experimental investigation in biology and biophysics. Sex-economy is defined as a scientific theory of sexuality in its biologic, sociologic and medical aspects. This is a laudable aim for a new journal and in spite of the cryptic nature of the term "orgone-research," one naturally wishes to know more as to "how it is to be applied." It is not encouraging, especially to those not familiar with the work of the patron of this new development, Wilhelm Reich, M.D., to meet such phrases as "character-analytic vegetotherapy," "seminal stasis" (accounting, *i. e.*, without further evidence for a plum-sized inflammatory mass in the epididymis); "pleasure is functionally

identical with a parasympatheticotonic plasma current in the direction of the periphery." One may reasonably object to the recommendation to practise masturbation in order to "achieve relaxation of the genital apparatus"; and to the recurrent emphasis on Reich's masterpiece, "Die Funktion des Orgasmus." Semantophiles, I fear, will search our dictionaries in vain for the meaning of "Orgone" (see p. 9 of Vol. I); fortunately, the special meaning to be attached to "sex-economy" has been furnished by the Editor.

Though first impressions are not favorable, one should perhaps reserve judgment on this pioneer venture, now settled in New York after having been chased about Europe by the Nazis. E. K.

UROLOGY IN WAR. By CHARLES Y. BIDGOOD, Chief Urologist, U. S. Naval Hospital, Washington, D. C. Pp. 76; illustrations. Baltimore, Williams & Wilkins Company, 1942. Price, $2.00.

THIS manual is described by the Surgeon-General of the Navy in a Foreword as a practical guide to officers in the field or in isolated places in dealing with urologic emergencies. He explains further that it is intended especially to aid those who are not specialists in urology. That it will fulfill these purposes in part is undoubted, but it seems to us that surgeons lacking training in urology would hesitate to apply some of the operations described.

This little book has 76 pages, the first 53 of which are largely devoted to descriptions of the pathology, symptoms and treatment of traumatic and inflammatory lesions of the genito-urinary tract. One gets the general impression that the subject matter was hastily assembled and arranged. The book is carelessly edited. The text contains much information that may be readily applied to urologic practice, but little attempt has been made to define measures applicable to various circumstances. Thus, under certain war conditions, urethral injuries may demand immediate cystotomy alone, in which event, there would be little time for study of the fascial planes of the perineum and pelvis, to detailed description of which 2 pages of the text are devoted. Nor does it seem to us that descriptions of the operative technique applicable to urethral strictures are particularly *apropos* to emergencies of urology in war. Among the few inconsistencies found is that dealing with the operative treatment of prostatic abscess; caution is at one time advised in the use of the urethral sound as a guide to drainage of such abscesses per perineum—no doubt lest the abscess be ruptured intra-urethrally—all of which is sound advice, whereas in another section, the performance of perineal prostatotomy employing urethrotomy and the use of Young's prostatic tractor, is advised for the treatment of such abscesses. The common concurrence of intra-abdominal and urinary tract injuries in war is justly emphasized. The section on traumatic injuries is as complete as could be expected, and the therapeutic measures advocated are based on sound surgical principles.

There would seem to be little justification for the page length discussion of the tabetic bladder, but the subject of bladder dysfunction after acute cerebral spinal injuries is well presented by Dr. Lloyd Lewis. Dr. Tovell's chapter on anesthesia is disproportionately long, but contains a good discussion of the various anesthetic agents and their use. There is every reason to believe that comparatively few anesthetic agents will be used in war surgery. With more careful attention paid to the relative importance of the various subjects together with their presentation in relation to their applicability under the varying circumstances encountered in war, the value of this manual would be considerably enhanced.

L. H.

SURGICAL PHYSIOLOGY. By JOSEPH NASH, M.D., Assistant Professor of Clinical Surgery, New York University College of Medicine; Associate Visiting Surgeon, Bellevue Hospital, New York City; First Lieutenant, Medical Corps, U. S. Army; Assistant Chief of the Surgical Service, Lovell General Hospital, Fort Devens, Mass. Pp. 496; 22 tables and 16 figures. Springfield, Ill.: Charles C Thomas, 1942. Price, $6.00.

THE importance of a comprehensive grasp of physiologic principles to the surgeon has come more and more to be recognized in the last few decades. The recent reduction in mortality and morbidity in surgical patients has been due in large part to the application of these principles in surgical practice.

Dr. Nash has chosen for this volume many of the physiologic subjects of most interest to the surgeon and has discussed certain of them in their relation to surgical problems. There is, however, a fair amount of material included that could be obtained from any textbook of general physiology and which is not, strictly speaking, surgical physiology.

Also it would seem to the Reviewer that in a book written for the general surgeon a more practical and pointed discussion of the physiologic aspects of anesthesia would be helpful.

It is to be hoped that this volume, with its many references to current literature, will find its way into the libraries of those doing general surgery.

I. R.

THE THERAPEUTICS OF INTERNAL DISEASES. Supervising Editor; GEORGE A. BLUMER, M.A., M.D.; DAVID P. SMITH, Clinical Professor of Medicine, Yale University, Consulting Physician to the New Haven Hospital; Associate Editor: ALBERT J. SULLIVAN, M.D., Adjunct Clinical Professor of Medicine, George Washington and Georgetown Medical Schools, Chief Medical Officer, Gallinger Municipal Hospital, Washington, D. C. Five Volumes, aggregating 4208 pages, with numerous illustrations. New York: The D. Appleton-Century Company, 1940, 1941. Price, $50.00 the set.

THIS is a monumental work, representing as it does a survey of therapy in all phases of internal medicine and also in border-line zones between internal medicine and certain specialties. Space does not permit mentioning by name the 55 contributors, yet such a recital would be sufficient to convince the reader of the quality of the text, for the most of them are well known as fruitful investigators in their respective fields. To arrive at his opinions, the Reviewer has used the volumes as a source for reference daily for several months and with highly gratifying results. He is impressed both with the excellence of the editing and the conscientiousness of the Editors. In spite of the broad scope of the subject matter, there is surprisingly little duplication and there appear to be no serious omissions. Appearing early in 1940, the first volumes contained some material that was out of date when the last volume was published late in 1941. So it was that although only 4 volumes had originally been planned, a fifth was issued repeating some of the topics covered in the first and second, such as the therapeutics of the sulfonamides and of vitamins, and endocrine therapy.

Volume I begins with a section on general therapeutics, including nutrition and dietetics, medical climatology, methods and uses of the various types of physiotherapy and of radiotherapy; specific serum and vaccine therapy, non-specific shock therapy, bacteriophage therapy, endocrine therapy, occupational therapy, psychiatric treatment. The second section deals with specific therapeutic techniques, such as oral, rectal, and various methods of parenteral therapy, transfusion, spinal puncture and paracentesis. Volume II includes a section on the pharmacology and toxicology

of the more important drugs, and a section on the general care of the patient during illness and in convalescence. The major part of the volume is devoted to the treatment of infectious diseases. Volume III continues with the treatment of infections and the diseases produced by fungi, metazoa and protozoa, by poisons, by physical agents; the treatment of derangements in water and electrolyte balance; pre- and postoperative treatment; the treatment of shock. Then follow sections on the treatment of diseases of the lower respiratory tract, of diseases of the blood and lymph vessels, and of heart disease and heart failure. Volume IV contains sections on the treatment of diseases of the gastro-intestinal tract, the liver, pancreas and peritoneum; the genito-urinary tract; nephritis; diseases peculiar to women; the blood-forming organs and the locomotor system. In Volume V are considered the treatment of diseases of the nervous system and of specific psychiatric disturbances; diseases of metabolism, diseases due to allergy; the common skin diseases treatable by the general practitioner. There are also sections in chemotherapy, endocrine and vitamin therapy, bringing up-to-date the material of earlier volumes. Each volume contains an index and in addition in Volume V there is a very thorough and satisfactory general index.

The wide range of subjects covered, the excellent balance in proportion and emphasis, and above all the generally high quality of the material combine to make this work an outstanding addition to medical literature. Its advantages for all physicians as a readily available source of reference are obvious. Its chief and unavoidable disadvantage from the standpoint of the young doctor is the cost. Hospitals would both help and be helped if they were to include this set in their libraries for collateral reading by internes and junior staff members. From every angle the work is heartily recommended.

R. K.

FROM WITCHCRAFT TO CHEMOTHERAPY. The Linacre Lecture, 1941. By SIR WALTER LANGDON-BROWN, Emeritus Professor of Physic and Fellow of Corpus Christi College in the University of Cambridge. Pp. 60. Cambridge University Press. New York: The Macmillan Company, 1941. Price, $.60.

THIS entertaining essay, after a graceful tribute to Linacre and St. John's College, Cambridge, as illustrations of the beneficent influence of tradition, proceeds to trace "the origin of witchcraft from primitive religion and the part it played in the evolution of remedies." Up through the local deities of tree and fountain to the gods of Egypt and Olympus, the "little people" and the witches of more recent times, the story leads to the nineteenth century development of modern therapeutics, in the last decade of which, for instance, "the first endocrine was given, the first antitoxin injected, while *x*-rays and radium were discovered." In the present century the development of the vitamins and of chemotherapy, exemplified by the arsenicals and the sulfonamides, brings the story up-to-date.

E. K

THE MEDICAL CLINICS OF NORTH AMERICA, VOL. 26, NO. 3, MAY, 1942. Symposium on Gastro-intestinal Diseases. New York Number. Pp. 336; 32 illustrations. Philadelphia: W. B. Saunders Company, 1942.

THIS volume presents a good résumé of present-day concepts of the etiology, the clinical and laboratory diagnosis and the management of many gastro-intestinal disorders. The problems of peptic ulcer, simple and complicated, including detailed therapeutic measures, are thoroughly reviewed. Gastritis, gastro-intestinal allergy, chronic constipation and diarrhea, spastic colon, tuberculosis of the alimentary tract, the common digestive dis-

turbances of infants and children, primary carcinoma of the liver, traction diverticulum of the esophagus and rectocolonic lesions are ably presented from the clinician's viewpoint. The rôle of gastroscopy in modern medicine is outlined. The differential diagnosis of the acute abdomen is discussed. A short section on the office treatment of hemorrhoids and a timely presentation of the psychosomatic manifestations of gastro-intestinal disorders, together with general principles of treatment, are included. The pathologic physiology of the gall bladder and bile ducts is considered, together with some general procedures helpful in the hygiene of the biliary tract. A section dealing with the more important laboratory aids in the diagnosis of gastro-intestinal disorders brings one up to date on the clinical usefulness of these procedures.

In addition to the sections on the various digestive disorders, recent advances in certain miscellaneous fields are presented. These include discussions of the syndrome of coronary insufficiency, an interesting presentation of the clinical features of cardiac aneurysm, recent developments in digitalis therapy, especially with reference to the use of the individual cardiac glycosides, the diagnostic use of fluorescin in certain circulatory problems, and lastly, the nature, metabolism and physiology of vitamin A, together with a consideration of the diagnostic tests and the clinical manifestations of vitamin A deficiency. J. N.

MANAGEMENT OF THE SICK INFANT AND CHILD. By LANGLEY PORTER, B.S., M.D., M.R.C.S. (ENG.), L.R.C.P. (LOND.), Dean Emeritus and Professor of Medicine, University of California Medical School; and WILLIAM E. CARTER, M.D., Director of University of California Hospital, Out-Patient Department. Pp. 977; 95 figures. Sixth Revised Edition. St. Louis, C. V. Mosby Company, 1942. Price, $11.50.

THIS reference book describes in full up-to-date detail the symptoms and therapy of the almost countless diseases and disorders which can affect the infant and child. All practitioners who deal with children will find a store of useful information here, discussing topics such as vomiting, diarrhea, nutrition, hemorrhage, prematurity, diseases of the various systems of the body, prescriptions, laboratory tests, and methods of performing scores of nursing manipulations and diagnostic maneuvers. Etiology and pathogenesis are not stressed. The index, important in a volume of this kind, is complete and adequate. The illustrations are numerous and well chosen. The fact that this book is now in its sixth edition since first published in 1922 speaks eloquently for its popularity with the profession.
I. W.

A STUDY OF THE BLOOD IN CANCER, With Special Reference to the Needs of the Tumor Clinic. By O. CAMERON GRUNER, M.D. (LOND.). Pp. 100; fully illustrated, including graphs and colored drawings. Montreal: Renouf Publishing Company, 1942. Price, 15/.

THE aim of this monograph, published under the auspices of the Archibald Cancer Fund, is to present the blood changes found in cancer cases and to show a pattern of changes which might constitute the guide to the diagnosis of cancer. Part 1 presents useful features in the morphologic examination of blood cells; Part 2, the author's method for evaluating the blood state and the effects of treatment, and a résumé of the features in the blood which he believes will assist in the diagnosis of cancer; Part 3 gives various other tests for cancer. Though the Reviewer cannot accept many of the deductions drawn (*e. g.*, that "cancer is most certainly not present if . . . . the neutrophil count is over 80%"), or even that a special pattern for cancer

blood can be demonstrated, he finds much of value in the observations presented by the author who has had great experience in these matters. We believe that this monograph demands serious study by all students of cancer. E. K.

NEW BOOKS

History of the School of Nursing of the Presbyterian Hospital, New York, 1892–1942. By ELEANOR LEE, A.B., R.N., Assistant Professor of Nursing, Department of Nursing, College of Physicians and Surgeons, Columbia University; Instructor in History of Nursing; Chairman of the Education Committee of the Alumnæ Association of the School of Nursing of the Presbyterian Hospital. Pp. 286; illustrations, over 50. New York: C. P. Putnam's Sons, 1942. Price, $3.50.

The Modern Attack on Tuberculosis. By HENRY D. CHADWICK, M.D., Superintendent of Westfield State Sanatorium, 1909–29; Tuberculosis Controller of the City of Detroit, 1929–33; Commissioner of Public Health of the Commonwealth of Massachusetts, 1933–38; Medical Director of Middlesex Tuberculosis Sanatorium, 1938–41; and ALTON S. POPE, M.D., Chief, Bureau of Communicable Diseases, Department of Health, Chicago, 1926–29; Deputy Commissioner of Public Health and Director of the Division of Tuberculosis, Commonwealth of Massachusetts. Pp. 95; tables, 8. New York: The Commonwealth Fund, 1942. Price, $1.00.

Clinical Cardiology. With Special Reference to Bedside Diagnosis. By WILLIAM DRESSLER, M.D., Attending Cardiologist, Israel Zion Hospital; Assistant Attending Physician, Brooklyn Hospital, New York. Pp. 692; illustrations, 108. New York: Paul B. Hoeber, Inc., 1942. Price, $7.50.

The Prevention of Deformity in Childhood. By RICHARD BEVERLY RANEY, B.A., M.D., Associate in Orthopædic Surgery, Duke University School of Medicine, Durham, N. C.; Attending Orthopædic Surgeon, Watts Hospital, Durham, N. C. In collaboration with ALFRED RIVES SHANDS, JR., B.A., M.D., Medical Director, Alfred I. DuPont Institute of The Nemours Foundation, Wilmington, Del.; Visiting Professor of Orthopædic Surgery, University of Pennsylvania School of Medicine, Philadelphia, Pa. Pp. 188; illustrated by JACK WILSON; 88 illustrations. Published and Distributed by National Society for Crippled Children in the United States of America, Elyria, Ohio, 1941. Price, $1.00.

This little book was written as a primer for medical social workers and public health nurses who usually are the first to come in contact with crippling disease. It should also be of considerable value to the general practitioner who is without special training in orthopedics. The material is well presented in a manner that can be readily understood. The prevention of many crippling diseases is stressed in a manner that should be of interest to workers in preventive medicine. The illustrations are semi-diagrammatic and present the various crippling diseases in a clear manner. D. A.

The Ophthalmic Formulary. Compiled by G. GRIFFIN LEWIS, M.D., F.A.C.S., Oculist to the Grouse-Irving Hospital, Syracuse. Containing the favorite prescriptions of prominent oculists from all parts of the world. Pp. 167. Springfield, Ill.: Charles C Thomas, 1942. Price, $3.50.

This is a worthless book, unless one is interested in a compilation of favorite prescriptions by the older generation of ophthalmologists. F. A.

NEW EDITIONS

A Textbook of Histology. By ALEXANDER A. MAXIMOW, Late Professor of Anatomy, University of Chicago, and WILLIAM BLOOM, Professor of Anatomy, University of Chicago. Pp. 695; illustrations, 562, some in color. Fourth Edition. Philadelphia: W. B. Saunders Company, 1942. Price, $7.00.

That the phrase "as dead as morphology," so frequently on the lips of the modern investigators of the cell, is unwarranted will be recognized after even a cursory inspection of this book. The advances made in histology during the past few years are epitomized in the excellent bibliographies appended to each chapter. As noted in the preface, revision was most extensive in those sections dealing with bone, nerve, spleen, and female generative system, and the eye. New figures have been added, particularly 9 photomicrographs. Perhaps in later editions the numbers of the latter may be increased at the expense of the drawings, for in the textbooks of pathology as well as in medical literature generally, photomicrographs are used almost exclusively. The student should learn, from his textbook, how to interpret the normal histologic photograph. The quality of the paper and print is excellent. H. S.

Handbook of Hygiene. By JOSEPH W. BIGGER, M.D., Sc.D., F.R.C.P.T., M.R.C.P. (LOND.), D.P.H., M.R.I.A., Professor of Bacteriology and Preventive Medicine, University of Dublin; Lieutenant-Colonel, Royal Army Medical Corps. Pp. 414; figures, 13. Second Edition. Baltimore: The Williams & Wilkins Company, 1941. Price, $4.50.

The contents of this book are subdivided into 25 chapters. The first, Vital Statistics: a brief consideration of the technique of reporting and evaluating population records, is followed by 12 chapters all of which deal with infectious diseases and the organisms involved. Then follow 5 chapters which may be grouped together as a section on "Environmental Hygiene"—Water, Food, Air and Ventilation, Disposal of Waste, and Environment being discussed. The headings of the remaining 6 chapters are Occupational Hygiene, Poisonous Gases, Maternity Infant and Child Hygiene, Personal Hygiene, The Assessment of Normal Health and the General Practitioner and the Public Health Service. The book is intended for medical students but should be equally useful to practitioners. It is well written, and adequate for its purposes. One must remember, however, that it is intended for use in Great Britain. A bit of translating would aid local understanding. H. R.

Synopsis of Materia Medica, Toxicology and Pharmacology for Students and Practitioners of Medicine. By FOREST RAMON DAVISON, B.A., M.Sc., PH.D., M.B., Medical Department, The Upjohn Company, Kalamazoo, Mich.; Formerly Assistant Professor of Pharmacology in the School of Medicine, University of Arkansas, Little Rock, Ark. Pp. 695; illustrations, 45 (4 in color). Second Edition. St. Louis: C. V. Mosby Company, 1942.

The author has revised and brought this textbook up-to-date. It is accurate, concise and can be recommended to the practising physician. It contains a good chapter on prescription writing and practical prescriptions are given throughout the text. The book contains the essential actions, uses and toxic manifestations of all useful drugs. P. D.

Aids to Physiology. By HENRY DRYERRE, PH.D., M.R.C.S., L.R.C.P. (LOND.), F.R.S.C., Professor of Physiology, Royal (Dick) Veterinary College; Late Lecturer in Physiology, University of Edinburgh; Examiner in Physiology for Royal College of Surgeons, Edinburgh, University of Glasgow and Pharmaceutical Society of Great Britain. Pp. 306; 63 figures, several tables. Third Edition. London: Baillière, Tindall & Cox, 1942. Price, $1.50.

This pocket sized physiology is intended as a concise epitome of the subject for use by students as an adjunct to the larger standard texts and as a "refresher" for postgraduates and others. It succeeds admirably in condensing physiology in the smallest possible space. S. G.

PROGRESS
OF
MEDICAL SCIENCE

SURGERY.

UNDER THE CHARGE OF
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HARRISON PROFESSOR OF SURGERY, UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA, PA.,
AND
C. G. JOHNSTON, M.S., M.D.,
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BACTERIOLOGIC ASPECTS OF THE PREVENTION OF INFECTION.

WOUND infection would not occur if bacteria could be kept out of wounds. Therefore, for the sake of directness and clarity, it has been elected to confine this review to the bacteriologic aspects of the problem, namely, measures to keep bacteria out of wounds, and measures to remove or kill them should they succeed in entering a wound.

The means by which bacteria may enter a surgical wound are relatively few. Barring faults in technique, contaminating organisms come from the air; the skin of the surgeon, the dresser or the patient; and from surgical materials.

Air. A mass of recent work has conclusively shown that air may act as a vehicle for transmitting virulent bacteria considerable distances. The recovery of pathogenic bacteria from the air of hospital wards and operating rooms is direct evidence of this.[1,7,18,35,64] The decreased incidence of wound infection, and of cross-infection in schools, contagious wards and surgical wards when steps are taken to lower the bacterial content of the air may be taken as indirect evidence.[2,8,19,30,37,58,61]

The control of air-borne infection depends upon the answers to the following questions: 1, What are the sources of pathogenic bacteria found in the air of hospitals? 2, Can the aërial spread of these bacteria be prevented by controlling them at their sources? 3, If the bacteria cannot be so controlled, what can be done once they are in the air to keep them out of wounds?

Sources. Two primary sources contribute pathogenic bacteria to hospital air. These are: first, patients with respiratory infections and nasopharyngeal carriers of virulent organisms; and, second, patients suffering from infections such as carbuncle, empyema, diphtheria, and lung abscess.

Individuals expel droplets of saliva upon talking, coughing, or sneezing. By this means pathogenic bacteria escape from carriers and patients suffering from respiratory infections. In the past, emphasis has been placed upon large droplets which travel only short distances[15,60] and were thought to spread bacteria only 6 to 10 feet. There is no doubt that these droplets are an important cause of infection when a surgeon or a dresser talks directly over an open wound.[15] Meleney and Stevens[34] and Walker[62] are among many workers who feel they have traced wound infections to this source.

Recently, however, Wells and his collaborators[55,56,57,59,60] have presented evidence which has revolutionized the concepts of air-borne disease. These workers have shown that when an individual coughs or sneezes, he expels not only large droplets which because of their weight fall quickly to the ground and have only a limited direct range of infectivity, but also smaller droplets which have different characteristics.[56,59,60] When a droplet is expelled into the air, it falls toward the ground with varying speed, depending upon its size and specific gravity, the presence or absence of air currents, the relative humidity and the speed of ejection. Many small droplets evaporate before reaching the ground and become tiny buoyant nuclei of particulate matter—the droplet nuclei. Their mass is so small in proportion to their surface area that they do not gravitate to the ground but remain suspended in the air and are wafted about for indefinite periods of time. These droplet nuclei are capable of traveling great distances. Wells and Wells[60] inoculated the humidifying water of a one-room air-conditioner in the basement of the Harvard School of Public Health with *Escherichia coli*. The building was not mechanically ventilated, but the investigators were able to recover *Escherichia coli*, presumably some of those inoculated, from the ends of every corridor up to the top floor of the three-story building where the concentration reached approximately 1% of that in the air-conditioned room. These observers have also determined the disappearance rates for 16 organisms which were introduced into the air by an atomizer.[59] Since *Staph. aureus* and *Strep. hemolyticus* are the chief offenders in surgical wound infections, it is of considerable interest to note that they survived 3 and 2 days respectively.

It is apparent, then, that both sick people and healthy nasopharyngeal carriers of pathogenic organisms discharge virulent bacteria in large droplets of saliva and in small ones which become droplet nuclei. The large droplets may fall directly into a wound or may fall upon bedding, floors, tables, and so forth, and after drying be wafted about as dust. The droplet nuclei remain in the air indefinitely and are inhaled by patients, nurses, doctors, orderlies and visitors.

The second source of bacteria which are transported through the air is infected discharges of patients such as lochia, pus from draining wounds, feces from colostomies, and ulcerating cancers. Only a naive individual could believe that these septic materials stay confined to the inner layer of dressings. It is quite obvious to anyone who has had any hospital experience that dressings become soaked through readily, that pus and feces frequently soil the bedding and run over the patients' skin and pajamas. Willits and Hare[64] have shown that the "whole of

the contents of the bed containing a patient suffering from an infected wound" may harbor virulent organisms. Miles *et al.*[35] recovered *Strep. hemolyticus* from the outside of plaster casts of patients treated by the closed plaster method and from the outer surface of dressings. These organisms may be transmitted to other patients by hospital personnel, but more often by the air as particles of dust. When a bed is made or when dressings are done, these dried bits of exudate are sent flying into the air to light on other beds, dressings and open wounds. Van den Ende *et al.*[51] recovered *Strep. hemolyticus* from the air of a room in which a bed was being made even though the patient was not in the room. White[62] was able to recover *Strep. hemolyticus* from the dust of rooms which had harbored parturient patients with *Strep. hemolyticus* infections 5 days after they had left. Furthermore, a person who swept such a room 5 days after the patient had vacated it developed a streptococcal pharyngitis.

Contaminated dust is thrown into the air by sweeping, as shown by Allison and Brown[1] who found the highest incidence of *Strep. hemolyticus* in the air during the hours when sweeping and bed-making were done. Miles *et al.*[35] found that the bacterial content of the air of hospital wards paralleled the dust content.

Control of Sources. Can the aërial spread of these bacteria be prevented by controlling them at their sources? Those from the nasopharynx may be partially but not absolutely controlled. Hirshfeld and Laube,[23] who designed an apparatus to test the efficiency of masks in preventing the escape of both large droplets and droplet nuclei from the nose and mouth found that very few bacteria are expelled by an unmasked person breathing quietly through either the nose or mouth. During talking, however, large numbers of bacteria escape, chiefly in large droplets. Conventional masks decrease this contamination appreciably. A masked person, however, expels more bacteria into the air when he talks than an unmasked one who remains silent. There is no practical mask available which will completely prevent the escape of bacteria from the respiratory tract of an individual who is talking, coughing or sneezing. Contamination from this source, then, cannot be completely eliminated at present. It can be greatly reduced, however, by observing silence as much as possible and by wearing masks when it is necessary to talk. In the operating room, the maintenance of silence is practical. On the wards, this cannot be accomplished, but it is possible to avoid talking during dressings.

It is more difficult to prevent contamination of the air with dust-borne bacteria derived from septic discharges of patients. It was noted above that bacteria may be recovered from bedding, the outside of plaster casts, the outer layers of dressings, from patients' skin and pajamas. Any agitation of these articles sends organisms flying into the air only to alight again on other beds, on the uniforms of attendants and on the floor. Sweeping, bed-making and other necessary activities send them flying about again.

Preventing this type of spread in the operating room requires planning and a thoughtful procedure. First of all, the operating room must be built without many corners and much fixed equipment to harbor dust. Second, there should be an ample supply of sterile air. Third, the

patient must be transferred from his bed to the operating table, anesthetized, placed in position on the table, and covered with sterile covers in an anteroom. Thus his dusty, bacteria-ladened bedding never enters the operating room. Fourth, the operating room staff must wear freshly laundered clothes.

Preventing the spread of dust-borne infection from wound to wound is even more difficult on the ward. Van den Ende *et al.*[51] advocate oiling the floors and blankets to prevent liberation of dust when beds are made and floors are swept. Even with this precaution, the ward housekeeping should cease an hour before dressing time.[35] The linen and blankets should be changed and laundered frequently. Furthermore, dressings should be done with care. The soiled dressings must be removed with no more agitation than necessary and placed immediately in a closed container to prevent the liberation of the millions of bacteria which they contain. A rigid dressing technique, embodying these as well as many other precautions was described by McKissock, Wright and Miles.[31] These investigators felt that strict adherence to this technique had produced a marked decrease in cross-infection.

Air Sterilization. It is obvious that it is not practical in the operating room or the wards to carry out in sufficient detail measures that will prevent absolutely the escape of bacteria from the respiratory tract or from patients' infective discharges. It has been necessary, therefore, to develop methods of killing bacteria suspended in the air, either as droplet nuclei or as dust.

The most widely publicized of these is ultraviolet light. Although the germicidal properties of ultraviolet light have been known for many years, it is only recently that this light has been employed to reduce the bacterial population of air.[17,60] Hart[19] has used ultraviolet light in his operating room at Duke University since 1935 and he is convinced that it is responsible for a marked decrease in wound infections. Overholt and Betts[37] also have reported on the uses of ultraviolet light. There is still, however, insufficient evidence to draw definite conclusions on the place of ultraviolet light in the operating room. While the evidence seems to be fairly conclusive that it acts by reducing the bacterial flora of the air, this is not certain. It is possible that ultraviolet light kills bacteria which have entered the wound from sources other than the air, such as the skin of the patient or the hands of the surgeon, or that it may act by making a wound more resistant to infection by virtue of the inflammatory reaction which it causes. The answers to these questions will determine whether it is necessary to radiate only the wound or whether the air of the entire room must be radiated. Furthermore, ultraviolet light is not a harmless agent. Kraissl *et al.*[28] have shown that it produces definite inflammatory reaction in the tissues and that prolonged exposure produces gangrene of guinea pigs' intestines. More work will have to be done before the place of ultraviolet light in operating rooms is established. In the case of contagious disease wards and pediatric wards, however, there appears to be evidence that it is of definite value in the prevention of cross-infection.[8,30,58,61] Here, also, final appraisal must await more evidence.

A second method of reducing the bacterial content of air is being studied, but has not yet been sufficiently developed to warrant widespread application. Trillat[47,48] reported that the bacterial content of

the air could be reduced by spraying germicides into it in the form of mists. These mists consist of particles approximately 0.5 micron in diameter. The particles are so small that a relatively insignificant quantity of the germicidal agent suffices to fill a room with invisible mist. The particles, furthermore, remain suspended as do droplet nuclei and barring evaporation remain in the air for considerable time. Theoretically, each small droplet contains the same concentration of the germicidal agent as the parent solution. When such a droplet meets a single bacterium, it destroys it. A number of investigators, among whom are Twort *et al.*,[40] Pulvertaft *et al.*,[42,43] Williamson and Gotaas[63] and Masterman,[32] have studied aërosols in detail. While there is some disagreement among these workers, they have laid the foundation for further study and have shown that sterilization of the air in hospitals, theatres, schools, etc., with germicidal aërosols is possible and may soon be within the range of practical application. Certain facts, such as the selection of germicides, the design of apparatus for their atomization and the establishment of standards of concentration in the air remain to be established. An aërosol to be suitable for use must be non-toxic, and non-irritating to man, lethal in the concentration in which it can be used for all pathogenic bacteria which may be present in the air, non-odorous, invisible, non-corrosive, non-inflammable, and must not leave deposits or coatings on walls or furniture.[63]

At present, aërosols are used to sterilize the air of laboratories, media, kitchens and food storage rooms. For this purpose, they are superior to ultraviolet light, for they fill all nooks and cranies while ultraviolet light travels in straight lines and cannot affect bacteria in the shadow of an object. [An important article by T. N. Harris and Joseph Stokes, Jr., on the sterilization of air in enclosed spaces by propylene glycol vapor will appear in our September number.]

Skin of the Operator. Hopeless confusion attended the efforts to determine the importance of the surgeon's hands as a source of wound contamination until Price[39,40] devised a simple and reliable method by means of which the bacteria on the skin may be counted and the effectiveness of various antiseptics and methods of scrubbing determined. With this method, several very important facts have become evident:

(*a*) Complete sterilization of the skin of the hands and forearms is so difficult that practical considerations render it an impossibility.

(*b*) When rubber gloves are worn, conditions on the skin beneath are markedly altered, so that the generation time of the bacteria remaining after scrubbing or washing with germicides is promptly shortened to 40 to 60 minutes, and the flora rapidly increase until it may exceed by far the normal limits.

To reaffirm the latter fact, the author[22] cultured gloves which had been worn for varying lengths of time. The comparative number of organisms depended upon the individual, the amount of perspiration in the glove, and the length of time it had been worn. The number recovered varied from 1000 to 1,000,000 per glove. Thus, an enormous number of bacteria may escape from a torn glove with a drop of sweat. Torn gloves emitting droplets of bacteria-ladened sweat are a more dangerous cause of wound contamination than the dust and air, since ordinarily only 50 to 60 bacteria per hour fall into a wound from the air.

[The question therefore seems to be whether the partial sterility of the ungloved hand is a greater or less hazard than the chance of the torn glove.—Ed.]

Devenish and Miles[9] have traced an epidemic of *Staph. aureus* wound infections to the flora of the hands of a surgeon. They investigated two surgeons in the same hospital who had a marked difference in their rates of postoperative wound infections. Both carried a virulent strain of hemolytic *Staph. aureus* in their nasopharynx, but the surgeon whose wounds became infected carried a similar strain on the hands. Tests showed that these organisms passed through the coarse linen (48 threads to the inch) sleeves of his gown, and also passed through holes in his gloves. Punctured gloves proved to be very common, especially in patched gloves. Batiste oversleeves plus close inspection and care of gloves served to prevent infections in patients operated upon by the surgeon bearing the virulent *Staph. aureus* on his hands. The insidiousness of glove punctures cannot be overstressed, since it averaged as high as 24.2% of 6585 gloves, and most of the punctures had escaped the attention of the wearers.

The link between the nasopharynx and the hands as sources of contamination is very close. It is possible that some of the wound infections previously thought to be due to droplet spray from the nose and throat may have come about because the surgeon harbored on his hands the same organism that he carried in his throat. Price[40] has shown that bacteria with which the hands constantly come in contact may become part of their permanent flora. Gillespie *et al.*[13] found that 43.4% of a class of medical students were nasal carriers of virulent strains of staphylococci, and 19.5% were skin carriers. Moreover, 12.6%, or 29.03% of the nasal carriers, carried the pathogen both in the nose and on the hands. To assign the cause of an infection to droplet contamination from the nose and throat of the operator *via* the air, one must first rule out the possibility of contamination from the skin of the operator by looking for the same organisms on his hands and looking for punctures in his glove. Just what proportion of infections is due to air contamination and what to the transmission from the skin of the operators remains to be proven. If punctured gloves should be shown to be the worse offender, radiation of air may not be necessary, whereas the practice of wearing extremely thin gloves may have to be changed. It is interesting to recall that Harvey Cushing, who had an extremely low incidence of infection in spite of his lengthy operations, always wore heavy gloves.

Skin of the Patients. More difficult, if not impossible, is the evaluation of the rôle played by the patient's own skin in the production of infected wounds. Although surgeons vary widely in their attempts to clean the skin of the patient and to protect the wound from exposure to it, there is little difference in their reported incidence of wound infection. Some surgeons take great care to cover the exposed surrounding skin of the patient with sterile pads, and paint it with a powerful germicide[3] while others make no attempt to isolate the skin adjacent to the wound, or to employ anything more in the way of skin preparation than simple removal of grease and dirt with benzene.[36] Similar results from such a variety of method seem to indicate that the skin of the patient is not as important as some other sources of contamination. The explanation

may lie in the distinction Price[39,40,41] has demonstrated between two grades of bacterial flora on the skin, namely, the transient and the resident flora. The "transient" flora vary from day to day in quality and quantity since they are composed of bacteria which have settled on the skin from its daily contacts. Therefore, they are scant on clean protected skin, and profuse on dirty, greasy, exposed parts of the body. Since the organisms are frequently imposed on or mingled with other foreign matter, they are easily removed with the grosser contamination in a few minutes scrubbing. The "resident" flora, on the other hand, are remarkably constant for a given individual. The bacteria composing this type are so tightly attached to the skin that theoretically $2\frac{1}{2}$ hours of continuous scrubbing with soap and water are required to remove all of them.[40] Such adherent organisms would not be easily brushed into the wound by the touch of an instrument or gloved hand, and if the patient's skin is properly freed of "transient" bacteria by adequate scrubbing and applications of germicides, the "residents" become a less important source of contamination. However, no one has been able to prove this contention one way or another, and safety dictates that the surgeon reduce the total flora of the patient's skin to as low a level as possible. This is especially true of exposed parts of the body where the "resident" flora may be partially composed of virulent bacteria as a result of a long contact with sources of these organisms.[40] Price[39] has outlined means of accomplishing this.

Surgical Materials. There is no reason why gloves, dressings, instruments, solutions or sutures should ever be agents for the transfer of bacteria to the wound or from wound to wound. Simple, inexpensive methods for the absolute sterilization of all of these materials have been devised.

Actually, however, these materials do occasionally serve as sources of contamination, since there is widespread discrepancy between available knowledge and current practice. Steam sterilization, for example, is generally regarded as a relatively fool-proof measure. The opinion is current that to insure sterilization it is necessary only to place the material to be sterilized in an autoclave and then to expose it to steam at a given pressure. Actually, there are innumerable details which must be attended to, such as proper wrapping of bundles, proper loading of the sterilizer, and adequate temperature control. When the basic principles of steam sterilization are not understood by those responsible for operating the sterilizer, one sees such dangerous violations as attempts to sterilize materials in sealed glass containers filled with air, attempts to sterilize vaseline and other oily substances with steam, attempts to sterilize tightly packed drums or packages of tremendous size. The most striking recorded example of the difficulties encountered by sterilizer operators who work by ritual rather than understanding is told by Dr. Kenneth Black.[4] Questioning the efficiency of a steam sterilizer, he placed a thermometer in the center of a tin of dressings. When the temperature of the steam in the sterilizer reached 240° F., that in the tin was only 160° F. Even after he had screwed down the safety valve and sterilized for an hour, the inner temperature was only 220° F. to 230° F. Thereafter, he tested many sterilizers and arrived at similar results with a large percentage. A nurse who did not believe

the thermometers put an egg in the center of each pack in a given sterilizer, and was astonished to find them raw at the end of the customary sterilization period.

Other operating room procedures are subject to the same criticism. There is frequently considerable lag between the available and the applied knowledge. This exists because surgeons have delegated the responsibility of preparing sterile materials for the operating room to nurses who, as a group, do not possess the information necessary to understand such work. The nurses are forced to work by ritual rather than by understanding. When people do not comprehend the reasons for their actions, they are bound to make mistakes, especially when new equipment and new demands require deviation from the standard ritual.

Space does not permit a discussion of the theory and practice of sterilization of surgical material; furthermore, such a discussion is not necessary for there are many excellent papers on this subject, among which may be mentioned those by Hoyt,[24] Hoyt *et al.*[25] Underwood,[50] Walter,[53,54] Meleney,[33] Spaulding[45] and Ecker.[10,11]

The point which needs emphasis is simply this: methods are available for the preparation of these materials, but they are not being employed, because surgeons by and large are leaving the sterilization of materials in the hands of nurses. If each hospital would appoint one member of the staff to familiarize himself with this subject, not only could many loopholes be closed but considerable money could be saved.

The Sulfonamides. Despite all precautions, bacteria get into clean surgical wounds. In addition, certain surgical incisions must be made into or through infected tissues and are unavoidably contaminated. Consider, for example, a wound through which an acutely inflamed appendix is removed. Accidental wounds are obviously nearly always contaminated with bacteria, though not necessarily with virulent types.[16] Thus there are three types of wounds in which bacteria are usually present and in which infection may and often does develop. The spectacular success of the sulfonamides in the treatment of certain established infections suggests that they might be employed to prevent infection of these wounds by their contaminating organisms.

The bacteria which are involved in the majority of surgical infections may be listed as follows: *Staph. aureus, Strep. hemolyticus, Escherichia coli, Proteus vulgaris, Pseudomonas pyocyanea* and anaërobic spore-forming bacilli.

Except in the case of *Strep. hemolyticus*, the systemic administration of sulfonamides while of some benefit has not been remarkably successful in the treatment of infections caused by these organisms. Would the prophylactic administration, either locally, systemically or in combination, be more effective? The mass of evidence both experimental and clinical which has accumulated in the attempt to answer this question is too vast to be reviewed here. Those who are interested must consult such papers as those of Reed and Orr,[44] Colebrook and Francis,[6] Hawking,[20,21] Pickrell,[38] Bonnin and Fenner,[5] Long and Ravdin,[29] Jensen *et al.*,[26] Throckmorton,[46] Harbison and Key[14] and Key.[27]

In spite of the volume of work that has been done, the problem has not been solved. The evidence seems to show, however, that the prophylactic use of the sulfonamides, especially locally, is of definite

benefit in preventing infection with at least some of the bacteria which commonly cause wound infection and when properly used do not interfere with normal wound healing.

The local administration is based upon the supposition that it will result in a higher concentration of a given sulfonamide in the wound than can be obtained when it is administered systemically only.

When a sulfonamide is administered systemically, the concentration in the wound is approximately that of the blood and since it is not safe to keep this above 10 to 15 mg. per 100 cc.; the concentration in the wound cannot exceed this amount. The concentration of a given sulfonamide which can be obtained in a wound is directly proportional to its solubility in tissue fluids and the length of time that concentration can be maintained is inversely proportional to its solubility in tissue fluid. Thus sulfanilamide which is extremely soluble provides a high local concentration for a short time while sulfathiazole or sulfadiazine, which are relatively insoluble, will provide a lower local concentration which persists for considerable time.

Hawking[20,21] has shown that sulfanilamide is absorbed and disappears from a wound in less than 24 hours, while sulfathiazole persists 4 or 5 days. Sulfadiazine remains in a wound even longer.

It has also been shown that sulfanilamide will diffuse slowly through dead tissue, but that sulfathiazole does this at an even slower rate. Furthermore, the high local concentration of sulfanilamide exists for only a few millimeters about the wound, for as soon as the drug reaches tissue with an intact circulation, it is "whisked" away and its local level becomes that of the body as a whole.[21]

These considerations dictate that in practice it may be well to employ a mixture of sulfanilamide and sulfathiazole or sulfadiazine. The sulfanilamide provides a high local concentration for a short time plus fairly rapid penetration of dead tissue. The other component serves to maintain a lower concentration over a period of several days. Whether sulfadiazine or sulfathiazole should be used is not established, but the evidence seems to be in favor of sulfathiazole.[20,44]

That the high local concentration which can be obtained by placing these drugs in wounds will serve to extend their range of usefulness beyond that already established by systemic administration remains to be demonstrated conclusively. At present the evidence seems to show that it will.

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OPHTHALMOLOGY.

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AVIATION OPHTHALMOLOGY.

THE experiences of the early years of the last war made evident the fact that not all soldiers were physically and mentally equipped for flying. According to Armstrong[1] (1936), it was noted that in some instances as many as 50% of the candidates for the air services suffered

from a neurosis during training. It was also noted that 90% of the accidents to graduate pilots were due to defects in the pilots themselves. Others have mentioned that of the remaining 10%, 2% were due to enemy action and 8% to plane defects.

These observations naturally led to the formation of medical units, both for pilot examination and for research in aviation medicine. Because of this development, the percentage of accidents due to pilot error in the Royal Air Force had been reduced to 60% in 1941. Following the last war, interest in research lagged, but in more recent years an increasing amount of work is being done. Some of this has related to aviation ophthalmology and an attempt will be made briefly to review part of it here. The increased speed, high altitude capabilities and the general importance of air power in the war have been the stimuli for much of this work. Despite the many changes, the standards for pilot qualification set up by Wilmer[24] and his coworkers are, in the main, still satisfactory. They also contributed many of the basic facts in research from which more recent work has evolved.

Visual Acuity. These standards for the armed forces remain at normal, or 20/20 vision, for new candidates. In civil aviation the tendency has been to lower these standards and the wearing of glasses is permitted. The trend would seem to be toward a further lowering of the standards for initial visual acuity where vision can be improved to normal with glasses. Visual acuity of 20/50, correctible to 20/20 in each eye, is now the minimum vision without glasses required for transport pilots. For private pilots, if the visual acuity is less than 20/50 it must be correctible to 20/30. In regard to visual fields, the confrontation method is required in civil examinations, while a more extensive examination is done by the armed forces at entrance.

Hayden and Goss[8] have reported that at the U. S. Naval Academy the average incidence of visual deficiency has been decreased from 8.18% (classes 1934 to 1940) to 2.86% (classes 1941 and 1942) by requiring some hyperopic reserve in all the candidates accepted. This has markedly reduced the number who have become myopic before graduation and whose training is wasted from the standpoint of the Government. About 1 diopter of hyperopia is the preferred amount in a candidate; over 2 diopters disqualifies. These observations are of interest where young adults are to be given expensive and time-consuming training in work which, for its pursuance, requires normal visual acuity.

A general darkening of the visual field is noted with anoxia. If oxygen is then given, a sudden brightening of the field follows. This is a universal observation. Beginning with Wilmer and Berens in 1918, a number of observations by various investigators were made on the effects of visual acuity of anoxia. The findings were variable. Recently McFarland and Halpern[13] found that changes in visual acuity with anoxia at high illuminations were negligible, while there was a large drop in foveal visual acuity at low illuminations. Their conclusion was that "so far as foveal visual acuity is concerned . . . . it is much more important that airplane pilots be provided with oxygen on night flights than during daylight flights." Work is now under way to determine at what level oxygen should be used during night flights.

Depth Perception. The importance of good depth perception to a flyer is obvious, and even with the best visual acuity and muscle balance, landings under certain conditions, such as on snow and water, may be hazardous. The factors involved in depth perception are well understood and are usually grouped into those inherent in the individual and those dependent on his environment and his past experiences with it. At the start of the last war, attempts were made to measure this ability by using the stereoscope in near vision. This was found to be unsatisfactory and, later, the Howard Dohlman apparatus was introduced and is still in use. This apparatus is stationed at a distance of 20 feet from the examinee and is an excellent test for stereoscopic vision at a distance. When used properly, it determines his inherent degree of ability to judge distance.

The known factors in faulty depth perception, as listed by Thorne,[20] are: (1) inequality of vision; (2) accommodative asthenopia; (3) heterophoria; and (4) convergence insufficiency. Using the Howard Dohlman apparatus, Deyo[6] found depth perception to be only 20% as accurate with one eye covered as with the use of the two eyes. This illustrates the disadvantage under which a pilot with only one eye or with strabismus labors.

That aniseikonia, or inequality in the image size of the two eyes, may affect depth perception unfavorably is easily demonstrated. That it is commonly a cause of poor depth perception as usually tested is very doubtful. With the testing of large groups of individuals with the Howard Dohlman apparatus, the ones who are not within normal limits almost invariably reveal defects in their ocular muscle balance, refraction or visual acuity which readily explain the difficulty.

Walker[21] recently investigated the superiority of binocular over monocular vision in depth perception in respect to the vertical or horizontal position of the stimulating object. He used an apparatus designed by himself with two 0.125 inch rods 2 inches apart at 22.5 feet from the eye piece. Both rods were movable by the turning of a wheel by the subject. His conclusions were: (1) binocular vision is superior in perception of depth when the stimulus is in a vertical position or at an angular displacement of not over 60°; (2) when the visual stimulus is horizontal the error of perception is as great for binocular vision as for monocular vision; and (3) under ordinary visual conditions secondary depth perception factors such as relative size, interposition and relative height above the line of vision apparently compensate for the lack of retinal disparity that is present when objects are horizontal. In another study, Walker[22] compared movement of the stimuli by hand and mechanically but did not find enough correlation to suggest that the mechanical was superior to the Howard Dohlman or hand type. His studies do not controvert the known facts in regard to depth perception.

Good muscle balance is of great importance to a pilot. If he has a high degree of esophoria, exophoria or hyperphoria, while he may fuse and judge depth fairly well under ordinary conditions, if fatigued he may suppress the vision of one eye or suffer from diplopia, usually the former. If he suppresses, his depth perception then becomes similar to that of a one-eyed person and is much inferior. If he suffers from actual diplopia, the results might easily be disastrous. The Army regulations

in this regard have been that depth perception must average 30 mm. or less on the Howard Dohlman apparatus. Esophoria (at 20 feet) of more than 4 diopters, if associated with a prism divergence of less than 4 diopters, disqualifies. Esophoria of over 10 diopters disqualifies even if diverging power is equivalent. Exophoria of more than 5 diopters disqualifies. Hyperphoria of more than 1 diopter disqualifies. An angle of convergence of less than 40° disqualifies. Gross deficiencies, such as strabismus and diplopia (except in extreme rotation) naturally disqualify.

Color Vision. This is of importance to any pilot because of the use of color in navigation lights, and it is of even more importance to the military pilot because of the use of Very pistols, flares and so forth in his work. The Ishihara test, or similar pseudo-isochromatic plates, is the most reliable for detecting all degrees of color blindness. Color blindness is detected in this test very frequently in individuals who had no previous knowledge of a defect. If a defect is found, the Holmgren yarn test is then generally used and, being much less delicate, eliminates only a few of those found by the Ishihara test and these have the more gross forms of color blindness. If the Holmgren test is passed, they are acceptable.

This method appears to work very satisfactorily as regards civilian and transport pilots. With reference to military pilots, White's[23] findings are of interest. We found that individuals color deficient as revealed by the Ishihara plates but able to select gross shades of red and green were deficient in 3 of the main requirements of the military pilot with reference to color vision, namely, recognition of Very pistol signals, navigation lights and map color shades. He found that navigation lights on a plane could be identified 1 to 4 miles farther away by normals than by the Ishihara failures.

The most recent review of color vision as it affects military fliers is that of Schwichtenberg.[17] He reviews the Young-Helmholz and the Edridge Green theories of color vision, gives the correct technique for the Holmgren yarn test and suggests a technique for the Williams lantern test which he feels simulates conditions of military operation more closely than do other tests of color vision. He advocates this latter technique, especially for testing questionable cases.

A common suggestion in regard to this problem has been that numbers be substituted for or added to colors as signals. That is, all green lights be made double lights, red lights single, and so forth. This, of course, is not at all feasible from the military viewpoint where colors have a multiplicity of uses. It might be possible with civilian aviation, but here, too, we have numerous signals and navigation lights, on and off the ships, which would make it a very difficult problem, and there are many more urgent ones at the present time.

As far as we have been able to determine, color blindness is of no aid in penetrating the usual types of camouflage. When one considers that if a landing field is next to a pasture which appears green from the air the landing field will be colored likewise, it can be seen that this offers no advantage to the color blind.

Black Out. Blacking out is well described by Ryan.[16] This is due to the blood gravitating downward from the pilot's head. It may occur when coming out of a dive, making a sharp turn, accelerating, and so

forth. It results in partial or complete loss of vision and the pilot may see anything from a red glare to complete darkness. The latter may be accompanied by unconsciousness, this occurring usually when forces greater than 4 G. are produced. ("G" refers to the acceleration due to gravity.) For instance, the effective weight of a 150 pound pilot at 4 G is 600 pounds. The first effect of G. is the feeling of being pushed into the seat of the machine, then of the abdomen being pressed downward. Then the visual fields begin to dim, this being followed by complete loss of vision, followed in some cases by unconsciousness. This will last up to 5 seconds, depending on the amount and duration of G. and the response of the pilot's vascular system to it.

Ryan[16] also mentions that it has been the experience of the British that pilots with low blood pressures react badly to abnormal movements in the air. Young[26] analyzed 159 fatal crashes and concluded that hypotension may be the underlying cause in many cases of pilot failure. Seventy-three pilots (45.9%) manifested some form of hypotension (a blood pressure of less than 110 systolic or 70 diastolic); of these, in 62 (85%) the official cause of the crash was pilot error. On the other hand, only 43% of those with normal blood pressure were involved in crashes charged to pilot error. Reports from England are that for every 4 pilots killed in combat, 6 lose their lives because of some other cause at home.

Young[26] states also that "if enough violent flying is indulged in, permanent damage can be done to the central nervous system as was witnessed a few years ago when 2 fatalities occurred on one of the larger aircraft carriers within a few hours after carrying out an extensive dive bombing exercise." In this regard, we observed a test pilot several years ago who had developed a right third nerve paralysis 2 days after making an exceedingly rapid ascent in a plane he was testing. The condition was improving rapidly when we observed him and he revealed no other central nervous system disturbance despite an extensive examination. He was advised to limit his activities but a short time later was killed in a crash the cause of which was obscure. His blood pressure when examined here was 120/70 on a single reading, and on this single reading he could not be classed as a hypotensive. However, one might conclude that once a vascular accident, no matter how minimal, has occurred in a pilot he should be grounded.

Dark Adaptation. Several years ago a number of articles appeared[9,10,11] suggesting that night blindness due to vitamin A deficiency was relatively common in the general population and could readily be produced experimentally. A large amount of literature on the subject has since accumulated[3,5,19] and the consensus among most ophthalmologists at present is that it is not common and that it is not readily produced by dietary restriction. In fact, other changes may occur, as in the skin, with no definite findings as regards the dark adaptation. Recently, Yarbrough and Dann[25] found no correlation between dark adaptation readings and the blood level of vitamin A. They suggest that blood determinations of vitamin A seem to be the most promising method of detecting mild avitaminosis A.

The following reports would seem to indicate that as regards pilots under ground conditions, poor dark adaptation is a negligible factor. This is not true, of course, under conditions of anoxia, as will be mentioned elsewhere.

Eighty pilots from a commercial air line were examined here by Sheard.[18] While the threshold was higher for a few than the mean for the group, none could be considered abnormal. The changes found for the most part could be correlated with the pilot's age. In none was there change enough to warrant a recommendation against night flying. That these were normal variations is further shown by the fact that there was no significant change following months of increased intake of vitamin A. Porter, Carlson and Henton[15] examined 65 pilots on the Birch-Hirschfeld photometer; none were found deficient. They then examined 34 non-fliers and found 1 below the minimum standard. Following this they examined the same group, using a luminous clock to get a rough estimate of dark adaptation; their results corresponded very well with the photometer readings. Now that we know that poor dark adaptation is not common in the general population, perhaps if any testing involving large groups is to be done at all, this method or a modification might be satisfactory. As far as is known, no routine testing of the dark adaptation of military pilots is now done.

Anoxia. As the brain, especially the cortex, is very sensitive to changes in oxygen tension, it is not surprising that the eye should react in a like manner. The circulation is similar and the optic nerve is essentially an extension of the white matter of the brain.

I shall enumerate briefly here a few of the changes which take place with anoxia as regards the eye and refer any one particularly interested in the subject to an excellent review recently published by McFarland, Evans and Halpern[12,13] which has a complete bibliography appended.

Among the ocular changes observed are exaggeration of muscle imbalances, a decrease in the range of accommodation and other effects which one generally associates with fatigue reactions of the central nervous system. In this regard, by photographic studies, McFarland, Knehr and Berens[14a] found that it not only took longer to read a given line but that the eyes did not coördinate as well at 18,000 feet. They also found that known muscle imbalances were greatly accentuated during anoxia[14b] and that the precision of ocular reactions in this was diminished. Other changes are: impairment of dark adaptation (Berens[2]), widening of the angioscotomata in the central visual field (Evans and McFarland[7]) and an increase in the caliber of the retinal arteries and veins (Cusick, Benson and Boothby[4]). With the administration of oxygen there is a tendency in all these effects to quickly return to normal, and if the oxygen is continued, in the case of the retinal vessels, they become measurably smaller than normal. Some of these changes due to anoxia may be noted at altitudes as low as 5000 feet but are much more obvious at heights of 18,000 feet and over. The occurrence of aëroembolism in the retinal vessels has not been reported to our knowledge.

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Editorial Note to Medical Authors: We wish to call the special attention of author-contributors and readers of this Journal to two of the most frequent errors that appear in our manuscripts.

The first—the misuse of "milligrams per cent"—is well covered on Page 53 of the American Medical Association's book entitled "Medical Writing": "Results of chemical determinations are frequently expressed as 'milligrams per cent' or 'grams per cent.' This means literally 'milligrams (or grams) per hundred milligrams (or grams),' which in most instances is not the information that the author wishes to convey. To insure accuracy a writer should specify the unit used, such as 'milligrams per hundred cubic centimeters' or 'milligrams per 100 gm.' If a number of values are (*sic*) given close together in a section or in a short paper, it usually is sufficient to supply 'per hundred cubic centimeters' the first time the phrase appears and to use merely 'milligrams' (not 'milligrams per cent') thereafter." We have become so weary of correcting this fault—and yet probably have overlooked it in many cases—that we are taking this means of trying to reduce it for the future. We hope that other journals, and especially the Journal of the American Medical Association with its large circulation, will also emphasize the point.

We should like to regard the word "consider" as indicating that the item is still under consideration or being meditated upon, *i. e.*, that no conclusion has been reached. This is usually the first meaning given by dictionaries for this word. We believe that, some dictionaries to the contrary notwithstanding, it is improper to use the word where a decision has been reached; in which case some such word as "think to be," or "regard as" or "believe to be" or "hold as an opinion" gives the more exact meaning.

THE EDITOR.